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# THE AMERICAN JOURNAL OF PHYSIOLOGY

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No. 1

## THE QUANTAL PHENOMENA IN MUSCLE: METHODS, WITH FURTHER EVIDENCE OF THE ALL-OR-NONE PRINCIPLE FOR THE SKELETAL FIBER

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Work on batrachian muscle already reported from this laboratory has shown that when electrical stimuli are applied to the surface of the sartorius over an area sufficiently minute, it is possible to bring under ob-

servation events which contrast strongly with the phenomena of gross contractility. The results as published may be summarized as follows:

The observations of Keith Lucas (1) that skeletal muscle, in simple contraction, responds in determinate, discontinuous gradients to relatively continuous change of stimulus intensity, have been verified (2). Like discontinuity has been found to obtain under continuous change of tetanic stimulation (2). The unit, or minimal entity, of function has been found by direct observation to be, as Lucas inferred, the individual fiber (3). The most conspicuous sign of fatigue in the locally excited muscle is successive abrupt elimination of individual fiber activity through rise of threshold (2). Conversely, the staircase effect is in similar case dependent to an appreciable extent upon accession to complete function of previously inactive fibers, through progressive fall of threshold (2).

The methods employed, heretofore only generally described, have naturally been subject to improvement and accretion in the progress of further work, and a stage is now reached where the technical results justify a more detailed account. With improvement in technique the graphic output has assumed an increasingly convincing character. The tracings reproduced, although introductory to a number of separate problems, are here presented as cumulative evidence of the independence on the part of individual contractile values toward change of stimulus or threshold.

#### PART I. METHODS FOR THE GRAPHIC RECORDING OF FIBER MOVEMENT

##### *Principles of Method*

The combined devices for recording are indicated essentially in the diagram, figure 1. The uncurarized preparation lies in a bath of Ringer's fluid. Upon the bared muscle surface impinges one end of a bent glass tube lying in a vertical plane parallel with the fibers. The interior of the tube, filled with Ringer's fluid, is continuous with the bath containing the preparation by means only of a terminal pore of less diameter than a single fiber. The other end of this active liquid electrode is led into a separate bath of Ringer's fluid in which is immersed the porous cup of an unpolarizable terminal. A similar terminal system is immersed at a convenient point in the solution bathing the preparation. The circuit is completed through a coil subject to alteration of position with respect to an appropriately varied magnetic field (primary coil or moving magnet). A fine globule of mercury rests upon the linear region



of the preparation made active by the unipolar stimulus at the pore. The globule is illuminated by a strong beam of light directed through a lens system, the vertically reflected rays being projected through a compound microscope to a photographic plate moving horizontally at right angles to the direction of fiber activity. The plate is also made to record the position of a second image, coördinate with the first, serving, as occasion requires, to record time periods or the extent of movement of the stimulating coil.

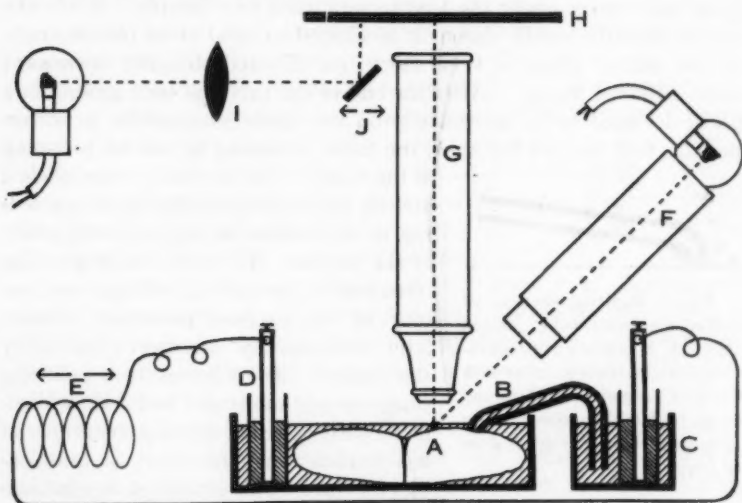


Fig. 1. Diagram to indicate essentials of the method. *A*, section of live preparation; *B*, active electrode, with pore in contact with muscle surface; *C*, bath of Ringer's fluid containing Zn-Zn SO<sub>4</sub> terminal; *D*, similar terminal in bath of Ringer's fluid covering preparation—the indifferent electrode; *E*, stimulating coil, movable with respect to magnet or primary coil; *F*, light-projector for illumination of mercury globule over *A*; *G*, recording microscope; *H*, photographic plate, movable at right angles to plane of drawing; *I*, lens system for projecting signal image on plate; *J*, mirror, movable with coil, *E*.

#### *The Electrodes*

The preparation and application of the pore-electrode were described in the first paper of this series (4). We shall review, however, certain points which have been modified in more extended practice. The electrode in present use differs from that first described chiefly in the form of the active, and in the mode of application of the indifferent, element.

*Active electrode.* In making the present bent form of pore electrode (fig. 2), soft glass tubing of about 2 mm. bore and 1 mm. wall is used, being cut to a length of about 3 cm. on completion. One end is first fused in a Bunsen flame until the closed lumen presents a perfectly sharp apex when examined with a strong lens. It has been found that with favorable material no drawing out (even by gravity) of the fused end is necessary to produce such an apex, which should converge at an angle as little acute as possible. An actually obtuse and seemingly blunt point may prove under the lens to terminate very sharply. While the end of the tube is still viscous it is allowed to bend at an obtuse angle to the shank, giving a very short arm directed obliquely downward when adjusted for use. After the end of the tube has been ground in a plane designed to lie horizontally on the tissue, and carried to within perhaps 0.01 mm. of the apex, the latter is opened by careful polishing



Fig. 2. Sagittal section of active electrode tube, actual size. *A, B*, surface of preparation in a direction parallel with fibers; *C*, region of wall ground away to facilitate observation or record from *D* of region close to pore.

of the facet. This should be accomplished strictly by polishing as distinct from grinding, as emphasized in Rayleigh's (5) study of the process. Even the finest grinding (removal by fine pitting) will mar the contour of the exposed pore and enhance later occlusion by particles retained by the jagged edge; whereas true polishing (approximate molecular removal) will effect a clean, circular opening sometimes of less diameter than necessary or practicable for use. The grinding, begun conveniently with the finer grades of emery or corundum cloth, may be completed with the finest grade of emery powder, the end of the tube being rubbed with a rotary motion over a plate of glass carrying the wet powder. The polishing is done in the main on a horizontal disk rotated by power, bearing a felt surface with rouge and water liberally applied. As soon as a facet of sufficient transparency is attained, the tube is placed under a high power of the microscope and the nearness of the apex to the surface ascertained by means of the fine adjustment used as a micrometer. Experience will decide as to whether to continue polishing or to repeat the last grinding operation. A number of such alternate procedures are often advisable, careful inspection being made after each polishing. It will finally be evident that only slight further polishing is necessary to touch the apex of the lumen and thus open the pore. At this stage, hand polishing is probably the safest procedure.

If the pore has been broached with sufficient caution, a few particles of rouge within the lumen will be the first indication of the event. These will probably firmly occlude the orifice, and it may be necessary to immerse the tube in aqua regia for many hours to clear it. This final forcing of the polishing medium into the pore is, however, probably of distinct advantage in giving the opening a smooth margin.

A polished surface of glass, according to Rayleigh (5) is an absolute condition—not one of relative fineness of grain, as with ground surfaces. Polish once attained cannot be improved; it is in fact an “all-or-nothing” effect, the microscope meeting a blank surface up to the limit of visibility. It is therefore readily to be understood that the pore in present use,  $7\ \mu$  in diameter, which is a particularly successful outcome of long continued hand-polishing, seldom becomes seriously plugged by foreign particles. The highest magnification shows a clean, circular pore in an unmarred surface. Since it opens, on the one hand, abruptly upon a slightly convex surface and, on the other, into a rapidly diverging conical cavity, an occluding particle, once dislodged from the pore, is at once free in either direction.

By preliminary shaping with a grinding wheel it is possible so to reduce the thickness of the glass on the distal side of the cone (fig. 2, C) that the pore will emerge very close to the edge of the facet and hence permit, if desired, observation or record of response almost at the point of excitation.

*Indifferent electrode.* In the method as originally described (4) the indifferent contact of electrolyte solution with tissue is located at the annular junction of the ends of two concentric tubes, the inner of which carries the pore. Both electrodal elements are thus carried together to the region of application, the theoretical advantages of which arrangement do not appear to concern the work in hand. Nor for present purposes does the plan of conveying the indifferent terminal to the tissue by means of a wick (3) seem to offer any advantage over the present method, which has the merit of simplicity combined with the greatest possible dispersion of current over regions not designated for stimulation. As already indicated, the porous cup with its  $\text{Zn-ZnSO}_4$  elements (the form employed being, together with its counterpart in the active bath, the Porter boot-electrode) is introduced directly into the large bath of Ringer's solution which covers the entire preparation.

*Principles of action.* Figure 3 indicates what may be regarded provisionally as the mode of stimulation by this method. The electrolyte conductor is continuous between the baths through the pore, where

density of current will be abruptly increased. The region of high resistance is, however, intensely circumscribed, and the relative freedom of conduction elsewhere therefore permits the use of extremely attenuated currents. The region of the tissue lying directly beneath the

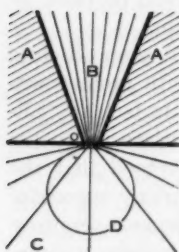


Fig. 3. Diagram to illustrate distribution of current density in pore region. A, A, section of active electrode tube,  $\times 250$ ; B, electrolyte solution contained in tube (active electrode); C, electrolyte solution of preparation bath (indifferent electrode); D, tissue (reduced to a circle of the diameter of a muscle fiber); o, pore. Density of current may be regarded as varying inversely with the distance between the radiating lines.

pore (for example, a superficial fiber) will be in surface contact with a region of current density greater than at any other point in the preparation; the degree of localization of effect being modified by the distance of the pore from the actual receptive surface. Thickness of fascial investment would play the greatest part in such modification and would account for the ease with which small groups of fibers are excited, as contrasted with the relative difficulty of securing single fiber response. Following the conception expressed in the diagram, it is obvious that any increase of current strength above that which excites only one fiber (minimal stimulus) will tend to bring likewise into activity fibers immediately adjacent laterally and beneath (submaximal response); hence the "steps" observed on gradation of stimuli over a sufficient range (fig. 12, a). The following postulates, moreover, would appear to be justified.

1. If the pore be cathodal with respect to the preparation bath, a stimulus of minimal value will, if the pore lie within the area of a fiber, excite that fiber alone. If it lie at the junction of two fibers both, if of equal threshold, will respond.

2. If the pore be anodal with respect to the preparation bath, the cathode for a given fiber impinged upon will be a lateral or deep margin where density of current is relatively low; and a considerably stronger stimulus must be used to excite. The use of a pole-changer in the stimulating circuit at once emphasizes the above assumption. Rarely do make-

shocks have to be considered in any range of stimuli employed by us, if the minimal stimulus be a break-shock.

#### *The Mechanical Stage*

The mechanical stage (figs. 4 and 5) is for the purpose of carrying preparation, baths and electrodes so that any point on the surface of



the preparation may be brought under the objective and properly oriented without derangement of the active electrode with respect to the tissue to which it is applied. A detached revolving microscope stage is centered under the objective and fixed to the table. Upon this is cemented a disk of heavy plate-glass, forming a turntable of 28 cm. diameter. Above and movable upon the turntable is a square of similar plate-glass supported by four stout corks. To this is clamped an ordinary mechanical stage with double rack and pinion, its carriage, however, being greatly extended by a glass plate, 16 x 21 cm., which on account of the weight it must support has its overhang riding on a  $\frac{1}{2}$

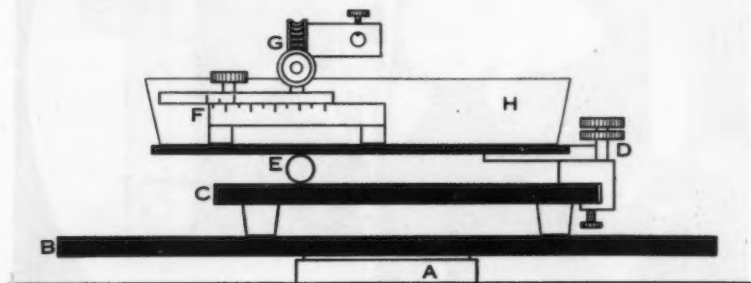


Fig. 4. Mechanical stage, front elevation,  $\times \frac{3}{10}$ . A, revolving microscope stage; B, plate-glass turntable; C, plate-glass support for attachment of D, mechanical stage proper, the glass extension of which rests upon ball-bearing at E; F, rack-and-pinion of electrode holder; G, worm-and-gear, carrying perforated extension with set-screw for electrode; H, container for preparation bath.

inch steel ball-bearing. This renders strain and friction negligible even with a heavily loaded stage.

The arrangement of the stage-load is shown in the photograph (fig. 5) taken from above. An electrode holder enables the pore to be lowered gently upon the preparation and carried laterally from fiber to fiber. Its adjustment mechanism consists of a worm-and-gear, carrying the electrode in a vertical plane, attached to a lateral rack-and-pinion. The electrode tube is further adjustable in a direction parallel with the fibers, by being passed through an opening in its support attached to the gear, where it is fixed by a set-screw.

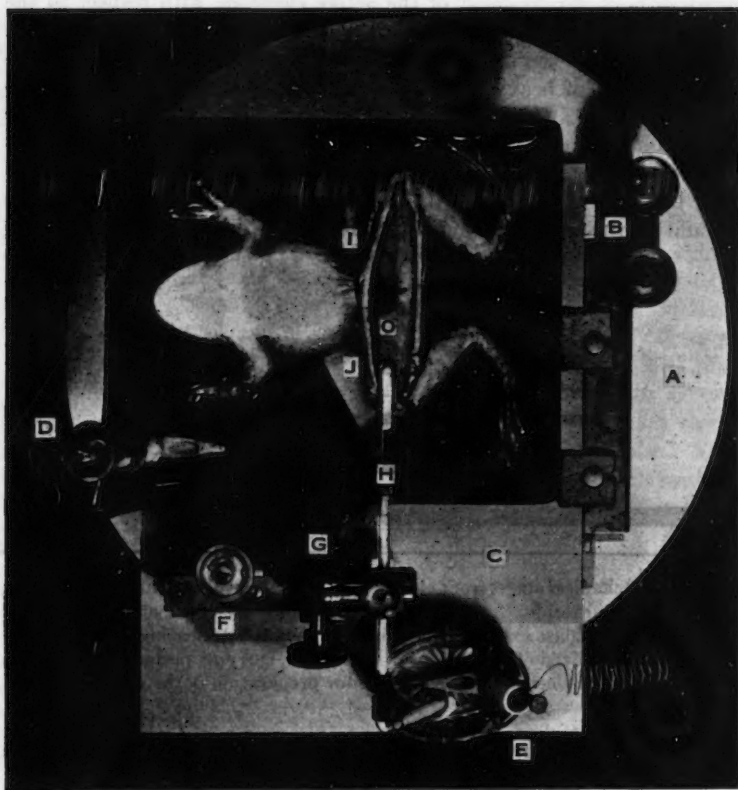


Fig. 5. Mechanical stage, loaded, photographed from above,  $\times \frac{1}{2}$ . A, turntable; B, adjustments of mechanical stage proper; C, extension of carriage; D, non-polarizable boot electrode (indifferent) immersed in preparation bath; E, boot electrode (active) in separate bath which also receives end of electrode tube; F, rack-and-pinion of electrode holder; G, worm-and-gear moving electrode, H, in vertical arc; I, J, plate-glass sinkers joined by cord over pelvis and supporting thighs horizontally. The pore end of the electrode is applied opposite J to the sartorius, and observations are taken at O, near the detached pelvic insertion.

### *The Mercury Mirror and its Illumination*

Particles adhering to a muscle are moved in accordance with the distortion of the connective tissue investment by the fibers beneath. The convex spherical mirror furnished by a globule of mercury is a ready means of recording such movement by photography. It is our practice to spray the preparation (usually the bared satorius *in situ* of the pithed frog) liberally with mercury ejected from a very finely drawn glass tube, by quick and slightly sustained pressure on an attached atomizer bulb. It is usually possible on stimulating a fiber to find somewhere on its length a globule of requisitely small size, moving nearly in the direction necessary for recording. The field is then properly oriented by means of the turntable and the stage adjustments.

The source of illumination is a 15 c.p. tungsten nitrogen bulb supplied from the building current through a transformer. The rays are focussed upon the globule chosen as an index through a lens system (figs. 1, *F*, and 6, *H*) with adjustable support. Owing to the spherical form of the mercury mirror the angle of incidence is immaterial over a wide range, making it possible, while maintaining a brilliant image on the globule, to keep the background free from disturbing reflections (fig. 18).

For certain earlier records a segment of fine capillary tubing containing mercury was used as a mirror with distinctive results (figs. 19 to 22).

### *The Fibromyograph*

The above term may be applied to the combined devices outlined mainly in figure 6. The purpose of the apparatus is to enable graphic records of fiber contraction to be made in a lighted room with choice as to speed of recording surface, to furnish a simultaneous graphic time-signal of desired frequency, or to indicate likewise graphically the changes in position of a secondary coil.

*Plate-glide.* This is built of wood in the form of a shallow trough without ends, and is mounted independently on three legs of heavy metal pipe above the mechanical stage and the microscope, the latter being carried on a rigid horizontal arm supported on a stand at the rear of the table, as previously described (4). Details of the plate-glide are shown in plan in figure 7, and in cross-section in figure 8. The plate-holder, of  $6\frac{1}{2} \times 8\frac{1}{2}$  inches capacity, carries four grooved blocks bearing on two glass rods serving as tracks. On these the plate-holder may be drawn from end to end of the wooden bed by means of a cord attached outside to the traction mechanism and playing over a cylin-





drical glass guide. A cord from the other end of the plate-holder passes in a similar way to a counterweight. The bed is transversely divided at its middle by a rectangular groove, the floor of which is perforated by a slot directly over the eyepiece of the microscope. The groove serves at one end as a recess and guide for a small movable box, open above and at its outer end, containing lens and mirror. This is the signal-box, to be described later. A cardboard cover fitted over the plate-glide is used to exclude light during a record.

*Traction piston.* For slow traction of the plate-holder the descent of a weight over an escaping column of air is utilized. A cord extension of the heavily weighted piston-rod of a tire pump (fig. 6) is carried over a guide to the plate-holder, the table being bored for the purpose. The exit of this pump is led to a horizontal cylinder which has two connections: one with the outside air through needle-valve *a*; the other, through needle-valve *b*, with a second pump used for filling the first. The first or traction pump being filled and connected, and valve *b* closed, the descent of the weight will be delicately regulated by adjustment of out-flow through valve *a*. By this means the length of the plate is transversed in a time ranging from 1 second to 30 minutes with sufficient smoothness and uniformity. At the lowest speed it is possible to record on one abscissa over one thousand separate and microscopically distinct contractions (figs. 36 and 37).

*Traction pendulum.* For rapid recording the plate-cord is uncoupled from the piston-weight and attached to a heavy and rigidly mounted pendulum (fig. 6) giving approximately a one second's single vibration when drawing the plate, and released by a suitable trigger. The moving plate-holder may be made to trip a stimulation-signal key sunk in the bed of the plate-glide (fig. 7, *G*).

*Time-signal recorder* (figs. 7 and 8). Mounted on a stand behind the plate-glide is a 15 c.p. tungsten lamp with compact filament, connected with a transformer and subject to adjustable resistances. Rays made parallel by a lens system attached to the back guard of the plate-glide traverse an opening in the guard and enter the signal-box already mentioned. Here they are converged by the lens mounted, with the mirror, in the box. The rays are then reflected vertically to their focus on the plate by the mirror, which consists in this instance of a fragment of coverglass with its back ground and blackened to leave a single reflecting surface. Interposed between the lamp and the first optical system is a celluloid diaphragm, the orifice of which is made with the point of a fine sewing-needle, rendering the image on the plate about the same



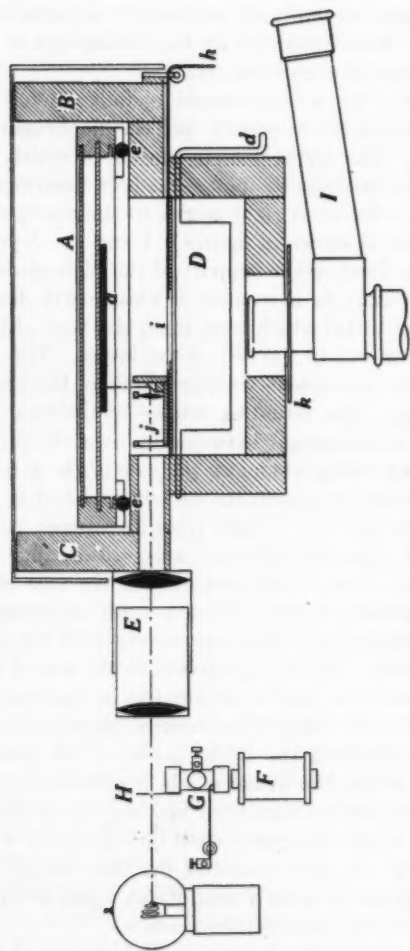


Fig. 8. Cross-section of plate-slide,  $\times 10$ . A, plate-holder; a, plate; B, front guard; C, back guard; D, shutter, actuated by lever, d; E, signal-light projector; e, glass tracks supporting plate-holder on grooved blocks. F, driving magnet of tuning-fork, G; H, diaphragm; h, signal-box cord; i, slot; j, signal box, projecting image defined by diaphragm, H, vertically to plate; k, flange; I, demonstration ocular (Leitz).

diameter as that derived from the mercury globule. The diaphragm is mounted on an electrically driven  $c''$  fork (512 d.v.). Illuminated at rest, it writes an abscissa (fig. 14) subject to interruption by various means (fig. 15) or records the ordinate position of the signal-box if this be actuated (fig. 14). When vibrated by the tuning-fork it traces on the plate a typical sinusoidal curve (fig. 34).

*Coil-position recorder.* When it is desired to indicate on the plate the variations in position of the secondary coil, the diaphragm described above is kept at rest. The signal-box, by means of which a spot of light is made to trace its path on the plate, has been mentioned as capable of movement in its recess at right angles to the movement of the plate. The construction is shown in figures 6, 7 and 8. A pulley actuated by a hand-lever is fixed to the support of the plate-glide and connected in such manner that its movement clockwise will draw toward the front a thin strip of metal which rests upon the floor of the groove and is perforated to conform to the slot of the latter. The signal-box is attached to this strip and resists traction through the tension of a contained helical spring. The actuating process at the same time lowers the secondary coil of an upright inductorium over the primary (fig. 6). Both attached cords being wound on the axle of the actuating pulley as a drum, the extent of movement of box and coil is the same. Hence any departure of the spot of light from its abscissa will indicate increase of stimulus in absolute terms of coil-position (fig. 14). The cord actuating the coil, after several turns about the axle above mentioned, is led to a suspended weight. Thus a ready adjustment of initial coil position is permitted by reciprocal movement of coil and weight while the pulley is at rest. The rays projected to the lens of the signal-box are sufficiently parallel to enable the focus to be maintained on the plate throughout the limited range of movement provided (8.5 mm.).

*Optical signal.* For studying the latent period of the muscle cell it has occurred to us to utilize the image of the response-index (mercury globule) itself as a stimulation signal, so moving the image optically that sudden cessation of its movement shall be coincident with stimulation. In other words, the rays from (for the time being) stationary object to moving image are to form a magnifying signal-lever devoid of inertia and operating on the contraction-abscissa.

The essential of the device (fig. 9) is a small rectangle of plate-glass interposed between object and objective. This is set in a metal frame pivoted to the objective and continuous with a light armature extending horizontally to the rear. When the armature is drawn upward

about 3 degrees by a small electro-magnet likewise attached to the objective, the prism is tilted through a very small arc; the rays from the object suffer immediate refraction in a plane parallel to the ordinates, and the image on the photographic plate, thus set in magnified motion, will come to an abrupt stop at the instant of contact of armature with core. The armature, however, bears as a contact surface a short piece of platinum wire soldered horizontally. Attached to the core of the magnet with non-conducting cement is a second platinum wire at right angles to the first. These crossed wires are introduced as terminals into the primary stimulating circuit (quite distinct from the magnet or

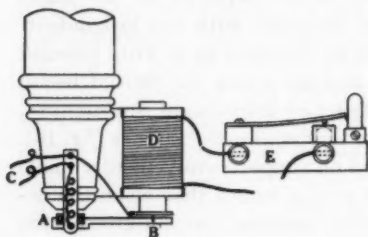


Fig. 9



Fig. 10

Fig. 9. Optical signal,  $\times \frac{3}{2}$ . A, square of plate-glass, mounted in armature pivoted below objective; B, armature carrying Pt contact wire; C, terminals in primary circuit, one in metallic connection with contact at B, the other with similar Pt contact wire fixed with a non-conducting cement to core of magnet D; E, Pt-Hg signal key tripped by plate-holder in mid-swing of pendulum, actuating magnet D.

Fig. 10. Focussing table,  $\times \frac{3}{10}$ . A, adjustable-focus magnifier; B, transparent glass screen; C, opening of slot-groove in bed of plate-glide.

signal circuit) and cessation of image movement is brought about by and coincident with their contact. Thus in the tracings (fig. 34) the latent period is measured from the summit of the first rise, emphasized by a slight recoil, to the beginning of the make-contraction. The course of events thus is: 1, movement of plate-holder; 2, knockdown of signal key by plate-holder, closing magnet circuit by Pt-Hg contact; 3, movement of optical signal; 4, stoppage of optical signal by making of Pt-Pt contact in the primary circuit—the instant of this stoppage of the refracted ray being taken as the instant of delivery of an induced make-shock to the preparation. In the records here published the stimulation key was closed by the pendulum itself and not by the plate-holder.

*Demonstration ocular.* One of the greatest aids to the successful use of the apparatus is a demonstration ocular (figs. 6 and 8, *I*). In observing an area of locally excited muscle we are dealing not always with one, but often with several thresholds, depending on the number of fibers in the field of influence of the electrode. By the use of this valuable accessory the experimenter is able to check the events in the field from end to end of the graphic record, and thus to control the conditions of stimulation by means of the mechanical aids. Moreover his adjustments may be automatically recorded through the signal mechanisms already described. Success or failure of a record is thus often determinable without first having recourse to development of the plate. The shadow of the adjustable pointer furnished with the instrument, to be moved at will over the field, can be placed so as to write beneath the record an abscissa (figs. 27, *A-F*, and 30) which has proved useful as a base for measurements of contraction and detection of contractures.

*Focussing table.* This is a simple but indispensable adjunct (fig. 10). A transparent plate of glass is mounted on supports conveniently made from small corks. These are made of such a height that when the device is laid on the bed of the plate-glide, bridging the slot-groove, the lower surface of the glass will be in the plane to be occupied by the film of the recording plate. A magnifier is so adjusted that when laid on the glass the lower surface of the latter will be in exact focus for the relaxed vision of the operator. The image of the light-reflex from the globule, thus magnified, may then be brought into extremely accurate focus by the use of the microscopic fine adjustment without recourse to a focussing cloth or other means of excluding the light of the room. The demonstration ocular is permanently adjusted for focus. By its means any loss of definition during a record may be approximately rectified by the observer.

*Rigidity.* Every precaution must be taken to secure rigidity of the entire apparatus, especially since any disturbance of the liquid surface over the preparation will introduce errors of refraction. Hence there are a large number of clamps and braces, not shown in the figures.

#### *Means of Stimulation*

*Stimuli for twitch.* A Porter inductorium has its secondary coil detached and suspended solely by the actuating cord (fig. 6), which is attached to the center of a bridge crossing the distal end of the coil. Very fine extensible wires lead from the coil to a fixed support, being



carried thence to binding-posts screwed to the table near the mechanical stage. The fact has been emphasized in a previous report (2) that considerable latitude of technical error in stimulation is possible when dealing with the muscle elements, without obscuring the determinate character of the response. A dry cell and sparking contact in the primary circuit will always yield determinate (fig. 13) and often uniform (fig. 12) responses, it being of course characteristic of the all-or-none mechanism that it is impartial toward a relatively wide range of excitation strength. On the other hand, to obtain uniform results in the neighborhood of thresholds requires great nicety of stimulation, quite beyond the capacity of ordinary methods of circuit interruption. For uniform or smoothly graded *influence*, as distinct from effect, we have resorted to special means. The best twitch effects (figs. 24 and 29) have been obtained by a mercury-mercury key, still in process of development, in which a conducting mercury column is broken within a rubber tube by an outside pressure-mechanism, automatically controlled. A key of the Martin type is of course thoroughly adequate if high frequencies and extreme mobility are not required.

*Magneto-inductor.* For the production of uniform tetanizing stimuli, brief or prolonged, we have found nothing so convenient and reliable as an extremely simple induction machine of a form already briefly described (2). The principle is by no means new, being a direct return to that employed by Pixii (6) who, in 1832, applying the new-made discoveries of Faraday, was the first to use the rotating magnet for producing currents in stationary coils.

Figure 11 shows semi-diagrammatically the details of the apparatus, in which uniform rotation of a light permanent bar-magnet is effected by an hydraulic centrifuge driven by a water-column of constant height. The column is provided by a 0.75 in. standpipe fed by the tap and overflowing at constant level beneath a 1 in. air vent into a waste-pipe. The motor is mounted for present use so as to discharge directly into a sink; the standpipe, attached to a chimney on the roof of the laboratory, receiving and feeding through two lengths of rubber hose led through the upper part of an adjacent window. The waste-pipe discharges into a building vent-pipe in the roof.

The two finely-wound coils influenced by the magnet are opposed and in series, and so connected that the circuit carries the jointly induced alternating current directly through the electrodes. The position of one coil, as well as that of its core, is adjustable with reference to the magnet, and is used in roughly approximating the threshold

stimulus. The core of the opposite coil is fixed; but the entire coil glides smoothly on glass ways over a metric scale. Fineness of gradation is attained by belting this coil over a system of pulleys so that one revolution of a large hand-wheel covers 2 cm. on the scale. This coil further registers its position on an empirically graduated quadrant through a 1:4 magnifying lever, enabling the observer controlling the wheel to read at a distance the coil-position in millimeters.

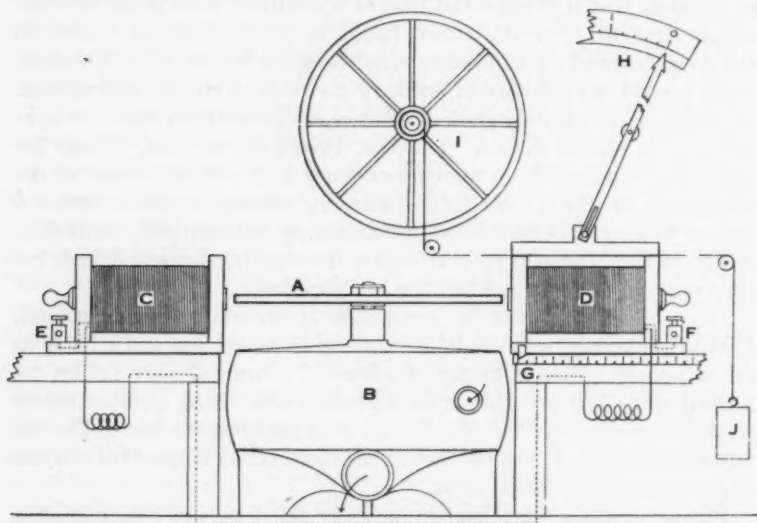


Fig. 11. Magneto-inductor (diagrammatic,  $\times \frac{1}{4}$ ). *A*, bar-magnet, 150 x 12 x 6 mm., rotated by hydraulic centrifuge, *B*, under constant pressure from stand-pipe. *C*, coarse adjustment coil; *D*, fine adjustment coil; *E*, *F*, terminals in electrode circuit; *G*, metric scale traversed by coil *D*; *H*, quadrant empirically graduated in terms of scale *G*, through  $\times 4$  magnifying lever. *I*, hand-wheel (relatively reduced) actuating coil, *D*, over reduction pulley; *J*, counterweight. The movement of coil *D* may be automatically recorded by connection of signal-box pulley (fig. 6, *x*) to an appropriate point on lever.

This apparatus, in conjunction with the pore-electrode, has been found to work with great uniformity. Experiments can be carried on all day without removing the electrode from the fiber beneath. It is particularly useful in exploring the muscle surface for favorable responding elements, determining threshold, and demonstrating contractions over the ocular-micrometer scale. Applied as a continuous tetanizer

it elicits clean-cut quantal effects (fig. 15) and admits of continuous and wide variation in stimulus-intensity (figs. 16 and 19). A simple metallic key makes and breaks the circuit without discoverable spark. A reduced record of stimulation-strength can be made on the plate by attaching the coil-lever near its fulcrum through pulleys to the signal-box, thus automatically registering the position of the coil relative to the magnet (fig. 16).

After trials with many different forms of stimulation, we have found this simple alternating current Pixii machine, placed in direct circuit with the electrodes, apparently the ideal mode of high-frequency excitation. The water column employed gives sufficient speed of rotation to completely tetanize the superficial fibers of the frog's sartorius (about 30 cathodal waves per second). By the employment of the bar magnet with its widely separated poles (15 cm.) instead of Pixii's horse-shoe form, the lines of force sweep through the coils abruptly on a relatively wide radius, yielding sharply-peaked waves of potential which are effective as stimuli with a current of extreme tenuity. The apparatus is kept permanently set up, and is ready for immediate service on opening the tap feeding the standpipe.

The coarse-adjustment coil, being always near the magnet, serves through its preponderating influence to maintain the form of the waves of potential, while the fine-adjustment coil, actuated over a wider range, alters their value slightly and with extreme delicacy. A telephone introduced into the circuit gives a pure musical tone and indicates clearly the continuity of the upward and downward gradients of excitatory influence. The exact form of these gradients is as yet immaterial. The ends to be achieved for present purposes are uniformity and reliability for any given coil-position, and a constant and self-maintaining driving mechanism, with absence of all sliding and brush contacts.

#### *Choice of Plates and Methods of Reproduction*

The form of photographic recorder described commends itself to a large extent in the fact that the tracings are made in a lighted room. This is possible from the protection afforded the plate-holder, first, by the bed and side-guards of the plate-glide; second, by the cover which is lowered over the device when the slide is removed from and restored to the plate-holder. For slow records with the traction piston we have found the slowest or "process" plates amply sensitive; but for the pendulum records a very rapid plate is necessary. The plates ( $6\frac{1}{2} \times 8\frac{1}{2}$  in.) are

cut lengthwise in two before use, giving strips of the right width to use in a standard projection lantern. For this form of demonstration the negative alone is of course as good as the derived positive. Enlarged positives are readily made by similar projection upon plates or developing paper (fig. 13). Direct prints often yield a record similar to a kymographic tracing, and are reproducible by line-cut (fig. 15). On account of the faintness of the more rapid portions of curves as well as the tendency of the partially illuminated field to leave a strip of "fog" as a background, the half-tone or similar process is usually required, as in most of the tracings here rendered.

#### *Conduct of an Experiment*

The following description sets forth the routine procedures as at present developed. A number of the tracings, however, were secured by methods differing in detail from those outlined in the text. Such differences, proper to various stages of the work, are indicated in the descriptions accompanying the figures wherever the departure is sufficient to require comment.

*Preparation of sartorius.* Although any parallel-fibered muscle preparation, if not too thickly invested, is adaptable to this method, the greatest convenience and most satisfactory results have been attained with the uncurarized sartorius, in situ and circulation, of a leopard frog of average size. This muscle, peculiarly adapted to the present work through its structure and thin investment, is also chosen advisedly on account of the mass of data already obtained through its study in the past, affording in the literature a safe basis of comparison. With respect to the disuse of curare, it is remarkable what liberties may be taken in this intensely localized form of stimulation without eliciting effects toward which the inhibitive action of curare is usually directed. Although a nerve-free region of the muscle is usually selected for application of the electrode, this is done largely for reasons other than the absence of nerve filaments,—comparative freedom of the fiber extremities from linear movement, primarily. Numerous experiments have been performed with the electrode on the mid-region of the muscle (fig. 13). Under a certain limit of intensity the stimulus, effective for superficial fibers, fails to influence the nerve elements; beyond this limit, however, a sudden dispersion of response reflects unmistakably an indirect stimulation. The hypothetical advantage therefore accrues of employing a tissue with all its susceptibilities chemically intact.

Brain and cord are destroyed as bloodlessly as possible; but if bleeding occurs from the pithing puncture it has been found best not to check it artificially on account of an apparent resulting motor nerve irritation. Suspension of the frog by the jaw for a few minutes until heart action is vigorous favors the capillary circulation in the leg muscles. The frog is placed in its container (a 4 x 5 in. developing tray), ventral surface uppermost, where it is anchored by two glass sinkers, 5 mm. thick, connected by a cord passing over the pelvis (fig. 5); the sinkers being turned underneath the thighs to support them in such a way that their ventral surfaces lie horizontally. The thighs are abducted slightly more than at right angles to the trunk. The skin of both thighs is now incised in a line which meets over the symphysis, and extends in the median line of each thigh to beyond the knee. The skin is turned back by carefully dividing the delicate tissue forming the lymph compartments on the ventral surface of the thigh near the pelvis and along the rectus muscles. These muscles, when detached from the pelvic origin, retract with little if any bleeding. The sartorius muscles will now lie exposed to view very nearly in a horizontal plane, favoring ready observation under the microscope from end to end. It has been found a decided advantage, where more nearly isometric contractions are not required, to incise the superficial sartorius fibers or even the whole muscle at the iliac origin. The resulting retraction not only renders the fibers more distinct (fig. 18) but greatly favors contraction in a straight line.

As soon as possible after exposing the muscles the tray is placed on the mechanical stage and the bare tissue sprayed with mercury so that the globules lie on the average about 1 mm. apart. The preparation is at once flooded with Ringer's fluid just sufficient in amount to cover the entire muscle surface. More elevated portions of the frog are covered with filter-paper in contact with the solution, which favors maintenance of peripheral circulation and prevents movements induced by drying.

The preparation made as above can be used for experiment at any time subsequently during the day, and is in fact best left undisturbed for a time to permit conditions altered by the operation to regain equilibrium.

*Setting up of electrode.* The pore electrode is kept in distilled water when not in use. In preparation for use the electrode and connecting tubes are filled with Ringer's fluid. To test whether the pore is clear, an atomizer bulb or hypodermic syringe is attached to the large end of

the electrode tube, the pore end dried with lens paper, and a slight air pressure applied. If a droplet of liquid does not appear at the pore, even under heavier pressure, the obstruction may be removed by one of the following methods, to be resorted to in sequence:

1. Apply considerable force after attaching the pressure tube to the pore end.
2. Completely fill the electrode and empty it abruptly through its large end by the same movement used in shaking down a clinical thermometer.
3. Place a drop of concentrated nitric acid for a few moments on the face of the electrode. Wash off and irrigate by pressure applied at the other end.
4. If the pore is badly obstructed the electrode can be filled with acid and pressure exerted preferably at the pore end. Irrigate thoroughly.

It is suggested that pepsin-hydrochloric-acid solution would be of service in certain types of obstruction.

To prevent siphonage during attachment of the tubes connecting the electrode with its bath, it is convenient to plug them in several places with cotton, avoiding the imprisonment of air. Glass-rubber joints are best not immersed on account of possible short-circuiting.

*Application of electrode.* The electrode must only gently touch the surface of the tissue; heavy pressure appears to inhibit activity of the surface fibers, permitting only of deeper stimulation. Insufficient pressure, on the other hand, allows the fibers to withdraw from effective contact on contraction, often resulting in a rhythmic series of contractions in response to a tetanizing current. At the right pressure any slight movement under the electrode due to contraction appears to introduce no variable factors. The proper tension is best gauged empirically on stimulation.

*Field of response.* Observation through the demonstration ocular under low power (e.g., Zeiss AA  $\times 2$ ) reveals the sartorius fibers with an apparent width of about 1 mm., with several mercury globules in the field of a diameter averaging about that of the fibers. Capillaries with circulating corpuscles are readily seen in various parts of the field. The electrode has been applied to a region where the linear sliding movement of fibers is not likely to be marked; such as at the tibial end, especially when the pelvic insertion has been incised. On stimulation with single shocks or briefly-held tetanic currents, the muscle is explored by means of the mechanical stage for a favorably responding region. Almost



invariably the fascial investment shows some movement in any field first observed, and the preponderating extent of movement on one side or the other leads the observer unerringly to the field of actual contraction. Here a fasciculus or small group of contiguous fibers, or even a single fiber, may be recognized in activity, the globules which happen to rest upon the active region showing preponderance in extent and straightness of movement over those which lie adjacent. If reduction of current to minimal strength fails to yield a sufficiently localized contraction, a slight shifting of the electrode laterally (to an adjacent fiber) or vertically (altering tension) will often bring a single fiber into activity. For most purposes, however, all that is desired is a clean-cut, straight contraction whether from one fiber or from several fibers acting as a unit. Observation at any region where the fibers curve or dip downward to their attachments, shows nearly always a curvilinear or aberrant contraction on stimulation (fig. 27), this being the resultant of asymmetrical elastic tensions opposing shortening. In nearly every instance a globule of mercury resting directly over an active superficial fiber will move exactly with the apparent fiber movement. Such a globule is selected as the recording mirror, and any neighboring globules within the field of the slot are removed with a hair cemented to the end of a glass rod. A good field for recording should have the following characteristics:

1. Globule about  $30\ \mu$  diameter, highly illuminated throughout its range of excursion, which should cover several quantal steps.

2. Movement in a straight line and horizontal plane; the latter in order to maintain sharpness of definition.

The small electric lamp used for illuminating is a nitrogen-filled bulb with a short coiled filament. The projector throws upon the field a parallel sided image of the filament and this is aligned so that the globule is well within the bright area throughout its movement. The last adjustment made in the demonstration-ocular field is directed toward aligning this area with the direction of contraction as finally corrected by means of the turntable during the focussing process.

*Focus.* Accurate focussing of the image reflected from the mercury globule is essential for a good record. In using the magnifier shown in figure 10 it is necessary to maintain a relaxed accommodation in its adjustment and use, and to check this by frequent reference to a scratch or other mark on the under surface of the glass table. If the focus of the demonstration ocular has been set to conform with the plate image, the eye lens requires no further adjustment for a given observer.

Owing to its greater depth of focus, however, it is inadvisable to use it in making corrections except during a record, when focussing from above is precluded. As a rule it is seldom necessary to make the latter corrections. The focus of the image reflected from the signal-box is permanently adjusted and needs only occasional verification. The needle-hole diaphragm, when vibrated by the tuning-fork, traverses the narrow image of the lamp-filament; hence care must be taken so to align the signal system that the diaphragm transmits light of equal intensity at the extremes of oscillation.

*Signals.* In using the tuning-fork, it is vibrated electrically until clear and steady in tone. The driving current is then broken and the pendulum record taken during the residual vibrations, which give a curve (fig. 34) undisturbed by the interference waves liable to occur from the vibration of supporting apparatus during the electrical actuation. If a time record of longer intervals, such as seconds, is required for slow records, the intensity of the lamp may be altered periodically by cutting out with a clock circuit a certain amount of interposed resistance, giving an abscissa broken into periods (fig. 15). Ordinate alignment of signal image with globule image is done at the time of focussing by bringing the latter into the required position with the mechanical stage. The alignment is checked for error photographically at the beginning of each record, as later described. The optical signal for recording the instant of a make-shock requires only connection, on the one hand, with the primary circuit; on the other, with the magnet or trip-key circuit. The trip-key, closed by the plate-holder in mid-swing of pendulum, is of course to be opened before each record. During a slow record the optical signal may be cut off from the stimulating circuit and the magnet operated by a hand-key to denote on the response curve the occurrence of various procedures recorded in the notes, such as modes of stimulation, application of drugs, etc. The signal was employed thus in figure 17, but is readily visible only on magnification of the original plate.

*Traction of plate.* The plate-moving devices, as are all others, are readily operated by the observer without assistance. In either piston or pendulum traction the plate should be started with the cord at full tension to avoid sudden jar. In using the piston, the escape valve (fig. 6, a), previously adjusted for the desired speed, may be connected to a long rubber tube, the outlet of which is released at the proper moment by the seated observer at the microscope.

*Management of plate-holder.* To load the apparatus, the plate-holder is placed in position on its tracks, with traction cord and weight-cord attached, and the cover is laid over the plate-glide, the end of the cover over the plate-holder being raised so as just to rest on the ends of the guards. The plate-holder is steadied with one hand while with the other the slide is quickly drawn; the cover now being immediately dropped in position. A low strip of felt at the end of the bed, against which the end of the plate-holder impinges, shuts out light sufficiently during this operation to safeguard "graflex" plates when the room is moderately lighted. The traction-cord is not hooked to the pendulum or traction-rod until everything is in readiness for a record. The shutter (fig. 8, *D*) is closed throughout the above preparations, and it should be seen that the flange (fig. 8, *k*) encircling the tube of the microscope is raised against the under surface of the bed after all focussing is completed. The end of a record is indicated by the arrival at the edge of the bed of a knot in the weight cord. This cord is used for returning the plate-holder to its original position, where the slide is replaced after lifting the edge of the cover. If a zero abscissa is required, a second exposure is made without stimulation. The two recording images are sufficiently separated to enable as many as six exposures to be made on one plate by carefully measured actuation of the mechanical stage between records (fig. 34).

*Record for correction of ordinate position.* Unlike the optical signal, the time and coil-position recorder is subject to error of coördination between response image and signal image. Such error is rendered determinable by taking a stationary exposure at the beginning of each plate record (fig. 14). This is done by stopping the plate just as it begins to cover the slot, opening the shutter and turning on the two recording lights. If the signal record is to be one of coil position, the actuating lever is moved through its entire quadrant, thus tracing a reference line for all positions of the signal image (fig. 24).

*Order of procedure.* The following points summarize in sequence the events of a typical experiment:

1. Preparation made, mercury globules applied and muscles flooded.
2. Pore tested and electrodes set up.
3. Illumination adjusted.
4. Recording area selected by trial stimulation.
5. Stimulation intensity range adapted to threshold.
6. Field oriented for alignment of direction of contraction and coördination of globule image with signal image.

7. Focus adjusted at plate level; shutter closed.
8. Electrodes, keys and signals circuited.
9. Traction mechanism set.
10. Plate-holder inserted and connected. Slide drawn.
11. Response verified and illumination of field corrected.
12. Traction cord connected to traction mechanism.
13. Plate drawn to slot. Shutter opened. Exposure made for record of signal-image alignment.
14. Traction released; observer at the microscope. Record taken and shutter closed.
15. Traction cord uncoupled; plate-holder returned to position of loading.
16. Abscissa drawn, if required, by repeating exposure under traction without stimulation.
17. Slide inserted and plate-holder detached from cords.

The amount of time required for the above series of operations is inconsiderable. When, in 1916, the first tracings were obtained by the photographic method, a full day was the time regarded as necessary for the attainment of a result. It is now possible, though not always advisable, to carry out the entire procedure up to a completed negative well within an hour. This shortening of time is the result of practice, improved technique and the fact that the bulk of apparatus can be permanently set up, ready for instant use.

## • PART II. FURTHER EVIDENCE OF A QUANTAL PRINCIPLE

### *On the Use of Terms*

The accompanying tracings have one characteristic in common: change in extent of contraction is for the most part conspicuously abrupt; and the transition is introductive of a new level which itself does not materially alter except abruptly—such gradual changes as make the latter a qualified statement being without known exception independent of alteration in stimulus intensity or threshold level. Recognition of these gradual changes thus serves to emphasize the dual character of muscular gradients—the continuous, and the abrupt or discontinuous. The discontinuous mode of gradient formation, reflecting as it must the accession or elimination of unit energy values, has been termed *quantal* by one of us in a previous paper (2). It is the most conspicuous character of activity revealed in a skeletal muscle by intensively localized stimulation; change of level is in steps. It is con-



Fig. 12. June 3, 1918; E. *R. pipiens*. Sartorius; tibial and pelvic tendons cut. Electrode (pore  $7\ \mu$ ) near pelvic end. Record taken near middle of muscle. Break shock every 2 sec. produced by pendulum of Powditch clock opening Pt-Hg contact in primary circuit. Dry cell, slight spark at pendulum contact. Rheocord and rheostat in primary. The first 20 twitches were recorded without change of stimulus. Thence the primary resistance was successively raised and lowered on the rheostat, introducing three limited series of which *a* shows perfect di-quantal gradients. Elsewhere there are variations out of grade to be ascribed to the crude method of interruption, but all are strictly determinate in terms of *a*. For the final series the resistance was continuously decreased to 0 on the rheostat, introducing a third quantal, the series being completed with uniform stimulation at this level. An initial continuous fatigue at the beginning of the tracing is emphasized by delayed plate movement.

This record is fifth in a series extending over several hours, of which figure 32 is the first. The threshold has risen to an extent represented by a range of 4 cm. on the rheocord. Continuous fatigue is apparent on comparison. Fatigue leaves all-or-none capacity untouched.

Contact print from original plate, actual size. Microscopic magnification,  $\times 13.5$ .

venient, therefore, to call the step-making mechanisms *quantals* since each manifests an energy value proper to itself—a physiological quantum. The term may, moreover, be carried over without ambiguity to designate the visual or graphic result of such determinate energy discharge, and we have found such usage greatly conducive to clearness and brevity in the description and discussion of experimental records.

A quantal may obviously be highly multiple, as in the ventricle, or simple, as in the striated fiber; or again, as in the "steps" of many of these records, double (from concomitant action of two fibers), triple, quadruple, etc. Compounding of quantals in varied degree is reflected in the graded character of skeleto-muscular reactions in response to varied stimuli and varied thresholds, the two effects being, as has been shown (2), reciprocal. The term all-or-none (all-or-nothing) as applied by Bowditch to the heart is therefore in the case of skeletal muscle strictly applicable to the single fiber only, or to the whole muscle after it has begun to be supramaximally excited. The skeletal *musculature* must be, however, as is the heart, quantal at all times and in any part taken; being constituted throughout, as is the heart, of all-or-none elements. Hence, were the heart at any time to suffer its assumed complete interconductance to become a function of stimulus or threshold it must still remain quantal by virtue of its elements. These conceptions may be summarized in a series of postulates:

In response to changing stimulus intensity or changing threshold level,

1. The fiber of skeletal, as of cardiac, muscle is all-or-none.
2. The normal cardiac musculature as generally considered is, owing to interconductance, likewise all-or-none; not so the skeletal musculature, owing to insulation of its quantals.
3. Both cardiac and skeletal musculatures, however, are quantal. The latter resembles the former in integral activity when the range of stimuli is supramaximal; the former resembles the latter in fractional activity if gradients of interconductance be assumed.
4. A quantal may appear as the single fiber system (absolute minimal contraction); as an intermediate multiple fiber system (submaximal contraction); or as a tissue system (maximal contraction, heart-beat).

#### *The Twitch of Fibers in Response to Varied Intensity of Stimulus*

Biedermann (7) has emphasized by a quotation from Fick a conception of extreme importance in the critique of such data as are here considered:



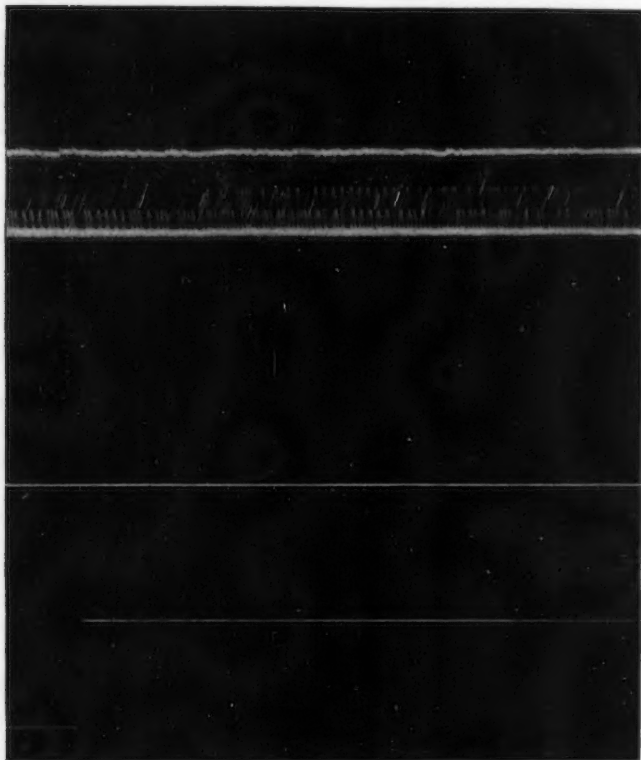


Fig. 13. Sept. 18, 1918; A: Tendons cut, electrode at middle of sartorius, record from tibial end. Break shocks by pendulum interruption, 1 per sec. The fluctuations in height of twitch reflect the crudeness of stimulation, the primary circuit being broken unevenly. The lower series was taken first and is subject to alteration in position of secondary coil as recorded in the lower signal record. The upper series was produced by stimuli of considerably greater intensity, as shown by the upper signal record, possibly exciting nerve filaments. Both are subject to similar adventitious irregularity of stimulation; the seeming turbulence of the upper series being, however, as measurement reveals, dependent upon the greater number of quantals involved as contrasted with the lower series, where the field of choice is limited to two. Transitory contractures appear in the upper series.

Plate record enlarged  $\times 5$ . Micr. mag.,  $\times 10$ . Total:  $\times 50$ . The plate contains about 2600 contractions.

This maximal limit is usually but little above that at which the first just perceptible contraction was yielded. The entire process of this greatest contraction and extension is known as a *maximal contraction*. It may be described in Fick's words by saying 'Each impact of excitation discharges either a maximal contraction or no contraction at all; it is only in a limited interval of the scale of excitation (often hard to find on account of its narrow proportions) that *sub-maximal*, so to say, imperfect, contractions are given.'

If the range of muscle activity as a function of stimulation strength be so narrowly limited, the same limitation would presumptively apply to the fiber unit. Assuming this, for the occasion, to share in all the apparent qualities of the muscle as a whole, we would expect to find a preponderating region of fiber response where, with respect to stimulus, a completely all-or-none régime would obtain—the maximal region, or region subject to maximal and supramaximal stimuli. The truth stated by Fick is one of common experience; the graded region of gross muscular response may, in highly irritable preparations, be easily overstepped and missed on the application of stimuli too coarsely graded. There is no reason to suppose that the single fiber, toward which very attenuated stimuli must be directed in order to localize the action, would reveal its assumed graded character with any greater readiness; in fact, it would be reasonable to assume considerable difficulty in so delicately grading the stimulus above subminimal that the region of continuity would reveal itself. That is, gradations of stimulus, fine for the tissue, might in similar increments be exceedingly coarse for the cell. The validity of this assumption was apparently recognized by Lucas (8) in the following words:

If any continuous gradation of the contraction of a single skeletal fibre can occur, it lies completely within a range of stimulus far smaller than that required to bring a whole muscle from rest to maximum activity.

Our own evidence against the assumption is partly negative, but cumulative. In the course of several years' observation we have never met with what we could regard as a region of continuity in fiber action dependent on change of stimulus, whether as the result of such change consciously applied, or of any adventitious change of the sort that must inevitably occur in electrical experiments. Attention has been called in a previous paper (2) to the significance of "crude" stimulation, in this respect—that in such crudeness lies a source of delicate as well as coarse variation. Hence the effect, in response, of such variations has been closely scrutinized. The contraction effect is variant; but all

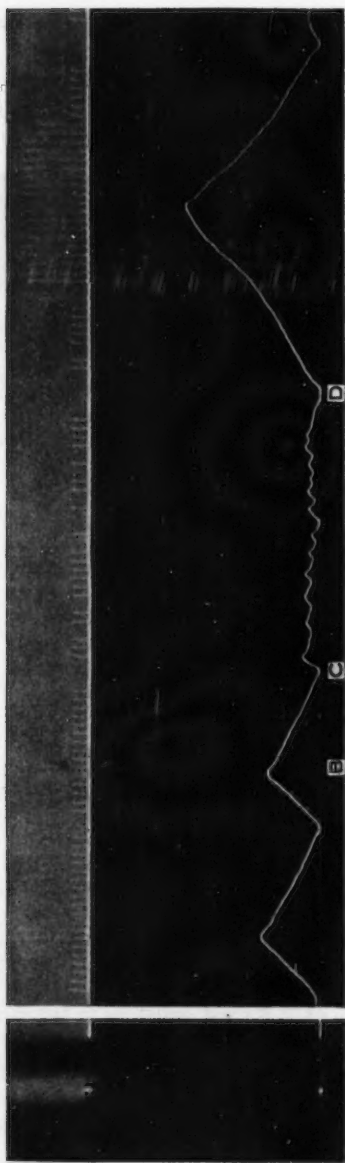


Fig. 14. Nov. 1, 1918; A. Pelvic insertion of *sa. torius* divided. Tibial end stimulated. The same preparation as shown in figure 5. Break shocks, 1 per 2 sec., of considerable uniformity as compared with those employed for the records in figures 11 and 12. Daniell cell; primary circuit interrupted by Hg-Hg key actuated by magnet circuit controlled by second's pendulum of Powditch clock. Detached portion of figure shows, above, mercury globe; below, signal image; plate at rest; the two images exactly aligned. The lower tracing records on the plate the actual changes in position of the secondary coil. The stimuli first increase in strength to a maximum and then subside, bringing into action a series of quantal twitches. The second series, B, shows a lower maximum. From C to D the threshold is explored by attempting to maintain the liminal stimulus. At D a new series is begun and carried to the extreme maximum of signal movement. The result shows that the maximum B is in reality an intermediate quantal which failed previously to differentiate. Thresholds are well maintained. The minimal threshold is roughly indicated by the trend of the exploration curve, C D. A strong light is required to resolve details.

Micr. mag.,  $\times 10$ ; total,  $\times 28$ .

variates are subject to precise repetition, and can be recalled at will by appropriate adjustment of current. Such determinate responses to relatively indeterminate stimuli may be regarded as characteristic of all tracings where especial precautions were not taken, as is the case in figure 12.



Fig. 15. March 23, 1918; A. The time is recorded in seconds by cutting out resistance from the signal light by means of a pendulum interrupter. The first part of the tracing shows several twitches produced by inductorium break-shocks. After the sixth contraction the electrodes were switched into the magneto circuit already adjusted for minimal brief tetani. The record now shows tetani of about 1 sec. duration followed by a prolonged tetanus, all with uniform stimulus. The tetani vary as do the twitches, giving one or both of two definite quantal values.

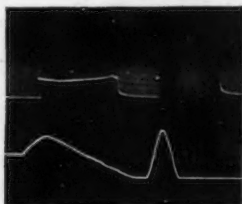


Fig. 16. Oct. 28, 1918; A. The lower curve records change in position of the fine-adjustment coil of magneto, a rise indicating approach to magnet and hence increase of stimulus (alternating current, about 30 cathodal waves per sec.). The upper tracing is of tetanic response, showing quantal composition. The first tetanus hesitates momentarily in its development (shown by a white dot close to the abscissa) at a low, probably minimal, quantal. This is apparently eliminated at the end, before the higher value subsides (shown by a slight notch). The second tetanus shows in its development three distinct quantal stages, the first of which is the maximum of the first tetanus. Continuous gradients, independent of stimulus-change, appear in both tetani.

Any region of continuity in the fiber, if it exist, must, as in the muscle, lie near the liminal value. Hence, as a more positive method of detection, we have resorted in many experiments to what may be termed *threshold exploration*, where the stimuli applied are consciously and repeatedly varied in both directions through the threshold at different

rates. Such a series of explorations is seen in figures 14, 17 and 29; and may in fact be recognized in all tracings where the stimulus is shown to linger in or traverse the threshold region (fig. 25), including those in which threshold has been the chief variable factor (figs. 23 and 32). The results are uniform. Stimulation change can create or destroy; it cannot alter.

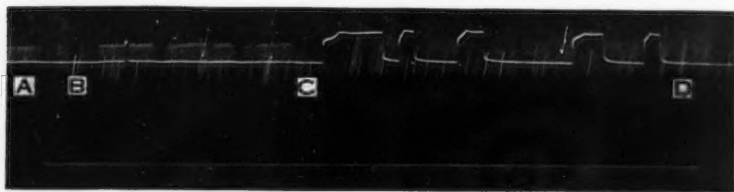


Fig. 17. Oct. 31, 1918; B. Break-shocks and brief magneto tetani produced automatically by Porter clock. A, twitches, 1 per sec. At B the optical signal was actuated three times (just visible on abscissa) to denote transition from twitch to tetanus. B C, brief tetani, 1 per sec., magneto coil in constant motion up and down the scale (fig. 11). C D, constant tetani, with similar movement of coil, fast and slow, as indicated in the varying duration of tetanus. D, optical signal. Following D, break shocks, as at A, failed to restore twitch. The signal record applies to twitches only. Direct print from plate, micr. mag.,  $\times 10$ . The tetani though apparently minimal all exceed the twitches in height, and vary in height with duration, except when prolonged. Their quantal character is seen in their common form and especially in their identical behavior toward diminishing stimuli—sudden elimination at a common rate of relaxation.

#### *The Determinate Character of Tetani*

Our work began with the study of tetanus, owing to the necessity of employing microtometer-scale readings in the earlier determinations. A fiber region was tetanized just long enough to read the excursion of an index-spot and, to exclude vitiation of results by possible staircase or fatigue effects, the excitation was seldom repeated oftener than once in 30 seconds. Such results have been plotted in a previous report (2). A graphic record of similar origin is shown in figure 21, where measurement of separate ordinates will show a determinate series. Other series of brief tetani are shown in figures 17 and 27, in the latter of which the duration of each tetanus is limited to the transit through a mercury contact of a platinum wire attached to a pendulum, cutting the alternating current into essentially twitch values.

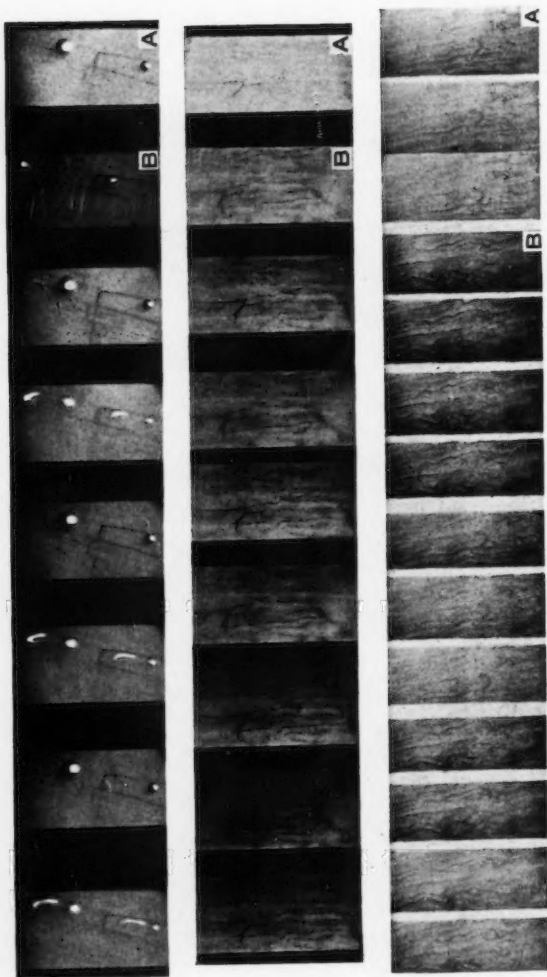


Fig. 18. Aug. and Sept., 1917. Surface of sartorius at rest and in local tetanus; stationary exposures. All three series read from *right to left*. Contact prints from original plates; micr. mag.,  $\times 13\pm$ . A, uncontracted; B, contracted surface. Electrode,  $7\ \mu$ .

The upper series shows alternate rest and movement of two mercury globules, the stimulus (alternating magneto current) lasting 1 second. Comparison of A with B shows immobility of one capillary arch in the presence of marked displacement of neighboring arches.<sup>1</sup> The stimuli were varied in strength.

The middle series shows alternately the excursion of a hooked vessel, giving an accurate index of the stress exerted by a straightening fiber to its right.<sup>2</sup> Stimuli varied in strength, each lasting 4 seconds.

The lower series shows two groups of three exposures, surface at rest, each followed by a group of four exposures, surface contracted. Tetanic stimuli of equal intensity. The determinate nature of the contraction is here shown by the uniformity of pattern presented by the crumpled fibers on either side of the straightened active fiber.<sup>3</sup>

<sup>1</sup> For details of this field, cf. Eisenberger (3), pp. 52-53. <sup>2</sup> Ibid., pp. 54-55. <sup>3</sup> Ibid., pp. 53-54.



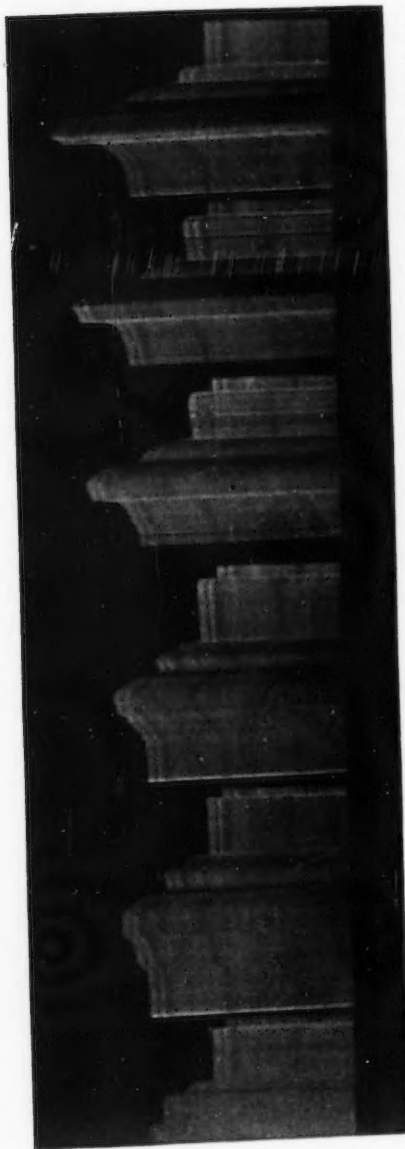


Fig. 19, Aug. 28, 1916: A. The record reads from right to left: the index mirror in this and the three succeeding figures was a column of mercury sealed in a capillary tube laid parallel to the contracting fibers of sartorius. For each series ("elevator" curve) a tetanizing stimulus (magneto) was applied with initial strength below threshold, and the coil continuously approached and then continuously withdrawn with reference to the magnet, covering 30 mm. and completing the cycle in about 3 sec. The plate was drawn by clockwork. Each curve begins at a level or step which represents the 0 abscissa, the duration of which varies with the time necessary for starting the coil slide mechanism. Each new level, always abruptly assumed, is complicated by continuous gradients (staircase or fatigue, both conspicuous in step 2). A repeated fall of threshold (quantal staircase) is seen in the high level at which the stimulus of initially subminimal value leaves the contractile state when cut off.<sup>4</sup> Contact print from plate. The faint, narrowly spaced abscissae are traced by the graduations of a micrometer scale in the ocular. Electrodes, about 50  $\mu$  for figures 19-22.

<sup>4</sup> For evidence of the localized character of activity in this preparation, cf. Eisenberger (3), fig. 6 and p. 52.



Fig. 20. Aug. 30, 1916. Method the same as in figure 19. Coil of magneto was moved continuously for each tracing, covering a distance of 60 mm. in each direction, over a time of 5 sec. The mercury column records itself at first in distinct lines, owing to irregular clockwork traction. The first quantal rise of the first and second tracings becomes the second of subsequent tracings, owing to the differentiation of a constituent quantal which persists as the minimal. Apparent fluctuation of threshold is reflected in the presence or absence of the higher quantals in the members of the series. Unlike figure 17, the final activity tends to regain the original abscissa. This and the two following records are to be read from *right to left*.

Figures 20, 21 and 22 are contact prints, slightly reduced; mier. mag.,  $\times 13$   $\pm$ .



Fig. 21. Record of brief tetani taken after that of figure 20. The first two lines (right) are the mercury column at rest, a stationary exposure being made of each with a 30 sec. interval. The subsequent images are subject to similar conditions; but the strength of tetanizing stimulus (duration, 1 sec.) increased 3 mm. of coil movement for every image in the series after the first up to a maximum, and then decreased by the same steps; covering approximately the same range as in each series of figure 20. Allowing for slight fluctuation of zero level, the quantals are well determined, though not always graded. That they are the same quantals elicited by the continuous method of grading stimuli may be seen by comparing the steps with those of figure 20, and also in the superimposed figure 22. The doubling of the image is due to a slight lateral movement of the active muscle surface, revealing the resting position of the column for each test to the left of the contraction position.



Fig. 22. Printed from the superimposed plates of figures 20 and 21. In spite of the wide difference in the time factors of stimulation, there is apparent identity of the main quantal values.

To return to figure 21, comparison is now to be made with figures 20 and 22. In figure 20 the stimuli, instead of being discontinuous, are continuous, up and down, over successive brief periods. The same quantals as in figure 21 reappear, but with marked continuous increments or decrements between steps. Such, however, prove to be less disturbing to the quantal hypothesis than might seem; for they frequently run counter to the gradient of stimulation obtaining at the time, as is graphically registered in figure 16. Moreover the superimposed curves in figure 22 show that the initial step-values persist.

That tetanic contractions are quantal is shown even more clearly in figure 15, where the corresponding twitch-values, empirically obtained, are present for comparison. The question of the existence of a tetanic increment over the corresponding twitch-value is a problem which awaits future consideration. It is sufficient for present aims to point out the indubitable fact of the quantal construction of tetanus, especially emphasized in the two curves of figure 16, where a certain hesitancy in the development of the limbs of the curves discloses the measured constitution.

The precision with which tissue patterns and contours reestablish themselves on repetition of a tetanizing stimulus is shown in three series of stationary exposures (fig. 18).

#### *The Quantal Factor in Fatigue*

It has been pointed out (2) that study of the fiber confirms the recognized principle of *threshold elevation* in the fatigue process; and that, moreover, the mere occurrence of such elevation must, in a quantal system, lead to a form of fatigue discontinuous in character. As thresholds rise above the stimulation level, the fibers having these thresholds must, if all-or-none, cease abruptly to function. This condition is present in figures 23, 31 and 32, and is to be repeatedly detected in others of the series. Nothing could be more inevitable *a priori*; and it becomes a very familiar phenomenon in the course of work with muscle elements.

#### *Quantal Facilitation in the Staircase Effect*

In figure 13 the reverse process presumptively occurs, and in figure 25 more convincingly,—an effect almost invariably met with when a preparation begins to respond after prolonged rest. The threshold suffers an initial fall, bringing into activity fibers erstwhile or otherwise



Fig. 23. July 26, 1948; C. Quantal fatigue. Break shocks, 1 per sec., rise in strength as indicated, introducing a series of uniform twitches, which persist for a time under uniform stimuli. After abrupt cessation of contractions a rise in stimulus fails to restore response. The only evidence of fatigue is rise of threshold leading to elimination of the quantal effect. The earlier contractions fail to appear in the cut.



Fig. 24. Dec. and Jan., 1918-19. *A*, mercury globule; *B*, signal-box test record taken with plate at rest. On comparison with the position of *A*, there is found to be a left-handed error of about 1 mm., which is to be applied in determining thresholds. The departures of the ordinate from the vertical are here insignificant. As the stimulus (break-shocks, 1 per 2 sec., mercury tube key) rises, a series of uniform twitches, *C D*, is induced, which ends as the stimulus again crosses the liminal point. Micr. mag.  $\times 10$ ; enlargement,  $\times 3$ ; total,  $\times 30$ . To be compared with the extended record, figure 25.





Fig. 25. Contact print from same plate as figure 24. *C D*, the region similarly lettered in figure 24. The contraction curves, all of which are identical with *C D*, have been filled with white under a lens for emphasis. It will be noted that as the stimulus falls from *D*, the twitches reappear at a lower level of stimulation; and the threshold continues to fall, as evidenced by several recrudescences. As the end of the record approaches, the threshold rises, and is finally restored to its first position. The process in other words has exhibited quantal staircase effect of one term followed by relative quantal fatigue. This is an especially convincing demonstration of the all-or-none law. Both stimulus and threshold have slowly and continuously changed and have discovered no intermediate energy system in any liminal region.

idle. This, too, would seem *a priori* inevitable; for when threshold, at first elevated, subsides to stimulation level an all-or-none system must enter with full energy discharge.

*Continuous Gradients in Fibril Response: A Contrast*

Even a cursory inspection of the tracings will bring immediate conviction that discontinuity is not the sole mode of functional change in muscle. Figure 30 is an extreme example of graded change within quantal limits. Every gap in response introduces a staircase effect; every persistent series, a continuous fatigue. Yet change of stimulus, which indeed must here be applied in order to parallel rising threshold,



Fig. 26. July 25, 1918; B. Break twitches, pendulum interrupter, stimuli 1 per sec. Secondary coil covered 20 mm. of primary at minimum distance (highest stimulus). The stimulus was raised slightly whenever a gap occurred in the series (rising threshold), the coil, with signal, being returned to zero position near middle of record, then raised and held as indicated. The series shows repeated elimination of the responding quantal (quantal fatigue), with a continuous staircase effect after each gap. Recrudescence occurs in groups in the latter half of record. Slight contractures are present. Contact print.

is impotent to alter these changes. Moreover, in spite of extreme alteration in the individual quantal capacity, the determinate nature of every step is relatively preserved, as reference to the description of the tracing will show. Thus, as expressed by Adrian (9) for the nerve fiber,

the all-or-none relation between disturbance and stimulus holds good for refractory as well as for normal tissue.

One familiar character of fatigue, in the muscle working as a whole under frequent stimuli, is conspicuously absent in our tracings. This is contracture, so-called—the progressive elevation of the base-line associated with delayed relaxation. Long continued twitch-series at one second intervals are repeatedly obtained with horizontal bases (fig. 31).



Fig. 27. July 26, 1918; B. From the latter half of a record showing in its earlier portion marked continuous staircase and fatigue. *A B*, brief tetani; *B C*, twitches, 1 per sec.; *C D*, brief tetani, 1 per sec.; *D E*, twitches repeated; *E F*, continuous tetanus held at uniform stimulation strength, breaking spontaneously into tetanic oscillations, becoming rhythmic at *F*. The twitches were produced by pendulum break-shocks; the brief tetani were cut in from the magneto circuit by same pendulum. The signal record indicates stimulus (secondary coil position) for twitches only. The abscissa *A F* was drawn by the shadow of the demonstration needle in ocular. Micr. mag.,  $\times 10$ ; enlargement from plate,  $\times 4.5$ ; total,  $\times 45$ .

Continuous staircase introduces twitch-series, *B C*. The tetani, *C D*, induce staircase and contracture. The twitch-series, *D E*, with its stimuli covering the entire range of the signal-box at two different continuous gradients, is conspicuously all-of-nothing. The tetanic oscillations, *F*, may be regarded as an example of quantal fluctuation (2). The quantal involved is a multiple one; at least several fibers are in action together throughout.

Occasional apparent exception is found, as in figure 36, *C*; but on the whole the fiber appears to be relatively immune to the delayed return so characteristic of batrachian muscle as a whole. The significance of this awaits solution.

On the other hand, very marked contracture is frequently to be observed in tetanus, if one may express by that term the relatively slow increment that succeeds the quick rise (figs. 17 and 19). It is sometimes of long duration; sometimes merged into fatigue. Its contractural character is to be seen in the fact that if degraded by the loss of a quan-



Fig. 28. Nov. 1, 1918; B. Large *R. pipiens*. Right sartorius, pelvic extremity cut. Tibial end stimulated just above tendon. Electrode pore,  $7\ \mu$ . Daniell cell in primary circuit. Twitches, 1 per sec. (break shocks), Bowditch clock working Hg-Hg tube-key. Contact print; first and last parts of record, 134 intervening contractions removed. Micr. mag.,  $\times 10$ .

The stimuli being in the threshold region (quantal fluctuation), the succeeding continuous rise and fall of stimulus introduce quantal gradients, with an apparent continuous fatigue at *A* (cf. fig. 29). The twitches fail abruptly (apparent quantal fatigue) just before *B*, and are restored by again raising the stimulus, which brings in another continuous decrement at *B*. Subsequently, for the remainder of the record, a slow continuous fatigue is seen in the quantal maintained by the maximum stimulus, with occasional spontaneous reversion to the minimal contactaion which is seen likewise to have shared in the fatigue.

tal (figs. 16 and 32) the amount of the increment tends to be assumed for the time being by the next lower step or, if the degradation be complete, by the base-line. Figure 15 is notable from the virtual absence of such increment.

#### *Fiber Recording as a Differential Method*

The reward of reduction to components in any complex system is a new instrument of analysis. One of us (3) has shown how, by the induction of fatigue in a multi-quantal system, the successive elimination of elements will reveal finally one, and one only, whose threshold still lies

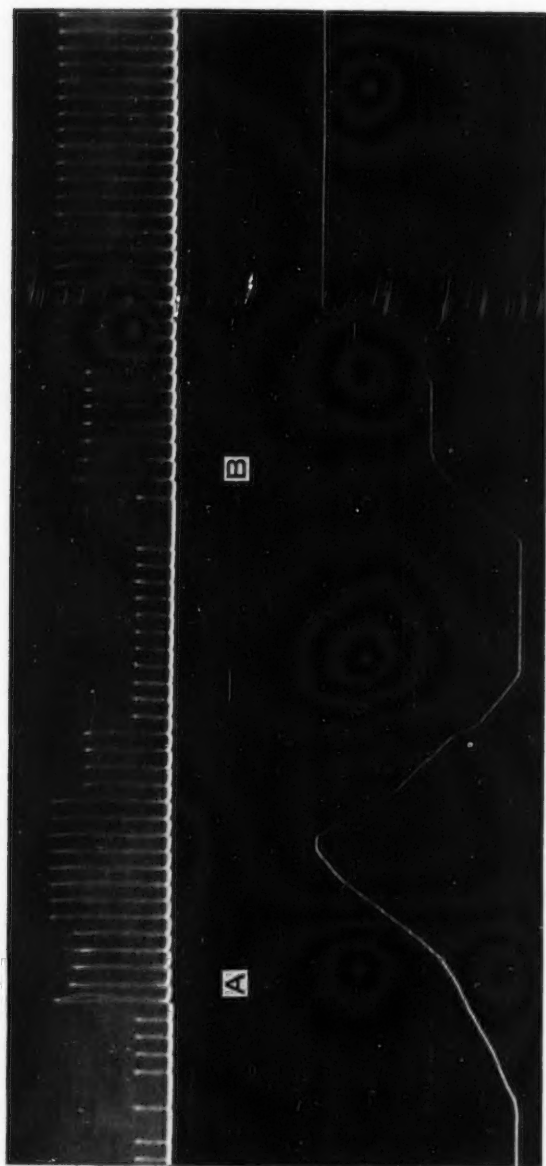


Fig. 29. Portion of figure 28,  $\times 33$ ; total  $\times 33+$ ; with corresponding lettering

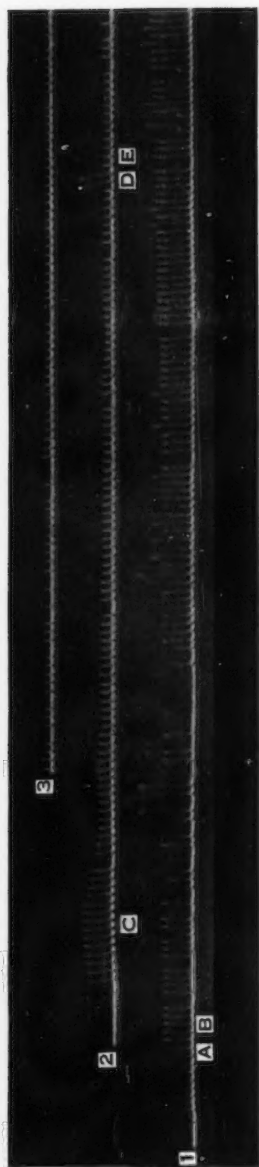


Fig. 30. Aug. 12, 1918; A. Intact sartorius; electrode at junction of tibial and middle thirds; recording globule 2 mm. from margin of rectus abdominis. Break-shocks, 1 per sec. by pendulum. The series 1, 2 and 3 consist of about 400 contractions each, and were taken in immediate succession. The lower dark band is an abscissa drawn by the shadow of demonstration needle. Micr. mag.,  $\times 10$ ; enlarged  $\times 3.5$ ; total,  $\times 35$ . First part of record only is reproduced.

Continuous fatigue is very marked. Study of the entire record shows an eventual progressive decrement of quantal  $B$  throughout, which is represented finally by the short contractions of series 3. Every gap, however, leads to a temporary recovery, the extent of which varies with the length of the gap. Thus in series 2, the group  $C$  is a recovery effect due to the short period of rest incident to returning the plate and adjusting for a new record line; it shows typical continuous staircase and fatigue, with a subsequent tendency to low undulations. That quantal characters are preserved is to be recognized as follows: Let  $b$  represent the quantity of the dominant contraction,  $B$ , and  $a$ , that of  $A$ , which is a higher quantal of which  $B$  is evident one constituent. If  $E$  actually represents the degraded quantal  $B$ ,  $D$  may be suspected of being a recrudescence of  $A$ , but with only the constituent  $B$  diminished by fatigue. Denoting the quantities of  $D$  and  $E$  by  $d$  and  $e$ , respectively, the relation above suggested will be

$$a - b = d - e$$

the assumption being apparently verified by actual measurement. (The summit of the first  $D$  has been accentuated. Measurement is best made from the second.) Further evidence tending to identify  $A$  and  $B$  with  $D$  and  $E$ , respectively, is 1, the recovery at  $C$  of the quantal to the original height at  $B$ ; 2, the characteristic backward trend of  $A$ , from lateral strain, reappearing in  $D$ . The strength of stimulus during the record was accommodated to the rising threshold.



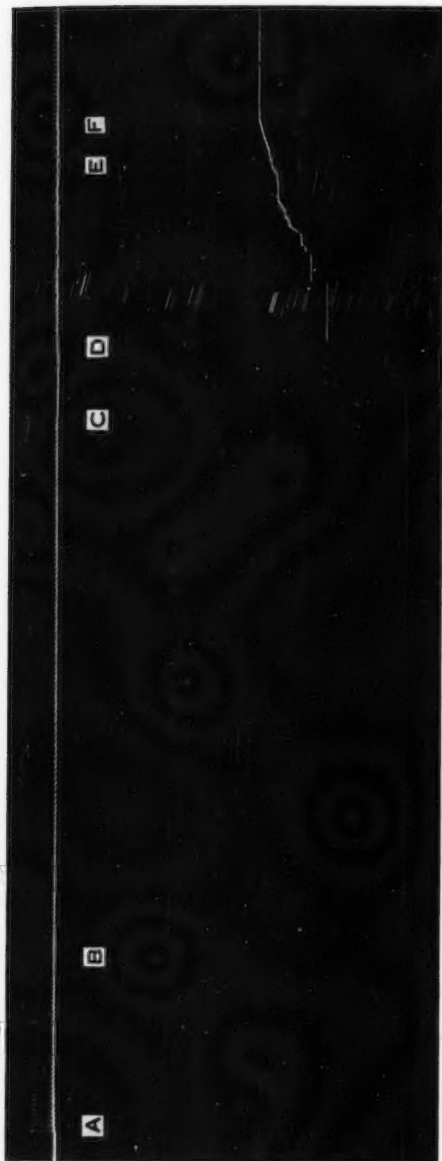


Fig. 31. July 26, 1918; A. Sartorius; circulation visible in superficial capillaries;  $7\ \mu$  electrode. Minimal break-shocks, 1 per sec., by pendulum interrupter. Micr. mag.,  $\times 10$ ; enlarged,  $\times 3.5$ ; total,  $\times 35$ .

The abscissa formed by the edge of the dark field is drawn by the end of the slot. A B, introductory fatigue with slight contracture, merging into a slowly developed staircase; uniform stimuli, as indicated in lower curve. At C the stimulus is no longer effective, and the quantal is eliminated until rising stimulus restores it at D. Subsequently it becomes necessary to continue the increase of stimulus in order to retain activity. Finally a new quantal is reached at E, representing an outlying or deeper fiber, and added to it as the contraction, E. From E to F only alternate shocks are responded to; and the response is a new minimal. At F the higher, compound quantal again appears; but at once gives place to a complete and even series of the new minimal. It is apparent that the first quantal composing the series A-E, long showing signs of failure, is at last completely eliminated, and that the additional factor in E and F now appears alone. This may be expressed by the equation,  $e - d = m$ ;  $e$  being the submaximal quantity (E, F),  $d$  the old minimal (A, B, C, D), and  $m$  the new minimal differentiated as the result of quantal fatigue. The deduction is supported by measurement of the several contractions in the region EF.



Fig. 32, June 3, 1918; A. See legend of figure 12 for experimental details. Pendulum break shocks, 1 per 2 sec. Crude stimulation; no deliberate change in intensity up to long gap near end, when rheocord slider was dropped 10 mm. decreasing primary resistance. At end, brief tetanus, followed by continuous tetanic fatigue curve (magneto). Contact print; micr. mag.,  $\times 13.5$ .

The series of twitches shows an introductory continuous fatigue, the submaximal value reverting to, and at length permanently replaced by minimal, which at length falls out by quantal fatigue (rise of threshold). Increase of stimulus only partially restores the series at end. The brief tetanus and the maximum level of the continuous tetanus evidently represent the submaximal quantal. The same minimal (now tetanic) is at length differentiated; this, finally, is itself abruptly eliminated.

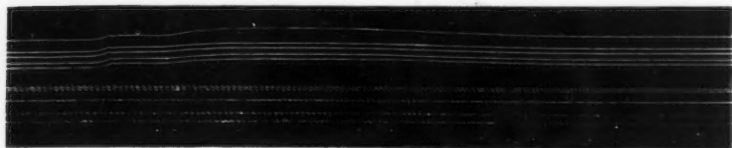


Fig. 33. July 18, 1918; A. Latent period. Sartorius; pelvic attachment cut superficially; capillary circulation active. Electrode ( $7\ \mu$ ) at tibial end; record near pelvic end; 5 exposures; 4 minimal contractions, 1 submaximal. The time curves (tuning fork moving signal diaphragm, 512 d.v. per sec.) correspond in ascending order with the contraction curves (make-twitches). The first summit denotes stoppage of optical signal by Pt-Pt primary make-contact. The stimulus was not altered except for the upper and last contraction (submaximal). Contact print; micr. mag.,  $\times 10$ .

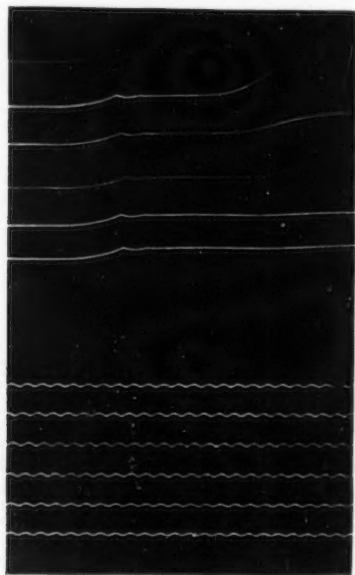


Fig. 34. July 19, 1918; D. Latent period. The description of figure 33 applies to this, except that the stimulus was increased in ascending progression. At least three different quantal values are registered.

beneath the level of stimulation. Such a process is now shown graphically in figures 31 and 32, where it will be seen that the process is by no means dependent upon fatigue of a continuous character. The remainder in such a series may or may not be the contraction of a single fiber. If irreducible, except by extinction, it is probably, in accordance with the first postulate on page 6, of either single or double quantal constitution.

That every quantal is a law to itself is clearly shown when fibers long in activity are compounded in action with others brought in by change of stimulus or threshold. The effect is a resultant which, in accordance with the dominance of one or the other, may exhibit staircase, fatigue or a virtual level. The chief example of this is seen in figure 37, which will presently demand special consideration.

#### *The Latent Period*

Reference to figures 33 to 35, included largely for the method, will show that there is here opened a fruitful field of enquiry. Biedermann (10), in his discussion of the latent period, reflects the generally accepted view that the period is, within the submaximal range, an inverse function of the stimulus intensity (Tigerstedt). The fact, however, which he also points out, that varying *maximal* stimuli do not control the length of the period (Helmholtz, Tigerstedt), introduces an interesting problem. It will be seen that no evidence is forthcoming from our results pointing to graded latent periods for a given quantal. It will also be seen that far greater refinement is necessary to make them of more than negative value. If the actual excitation process be of sufficient duration to contribute to the period as a measurable quantity, the all-or-none character of the response concomitant must have the simplifying value of a constant and hence negligible factor in the problem.

#### *Muscle Phenomena, Real and Virtual*

The object of this paper has been primarily to introduce the details of a new method; and secondarily to furnish as firm a basis as possible for an application to future problems of a conception of muscle activity which renders the gross phenomena, so long studied, necessarily subject to a certain amount of re-interpretation. Such re-interpretation, we believe, must take cognizance of two very distinct modes of altering mechanical effect. To what extent are gross muscular gradations to be



Fig. 35. The same preparation as in figure 34. Six minimal contractions superimposed, the time-curve applying to the first one recorded. The stimulus was increased for each response, but kept within minimal range. The apparent all-or-none effect is negatived as evidence by the failure of the optical signal exactly to synchronize, thus leaving in doubt the synchronism of the contractions.



Fig. 36. Sept. 16, 1918; A. Sartorius, deeply severed at both extremities. Record taken 3 hours after completion of preparation; capillary circulation stationary. Electrode ( $7 \mu$ ) about middle of muscle; record near pelvic end. Approximately 4000 twitches (pendulum break shocks, 1 per sec.) are traced on this plate over a combined recording period of more than an hour. The two records of secondary coil position are continuous, and apply to the two lower contraction series, the upper series continuing with the maximum stimulus recorded. Contact print; micr. mag.,  $\times 10$ .

Marked continuous gradients are present (staircase and fatigue). Contracture is little in evidence except at C in the middle series. At A-B a remarkable differential effect occurs, apparently spontaneous (cf. fig. 37), the stimuli for this portion of the series remaining unchanged so far as known and recorded.

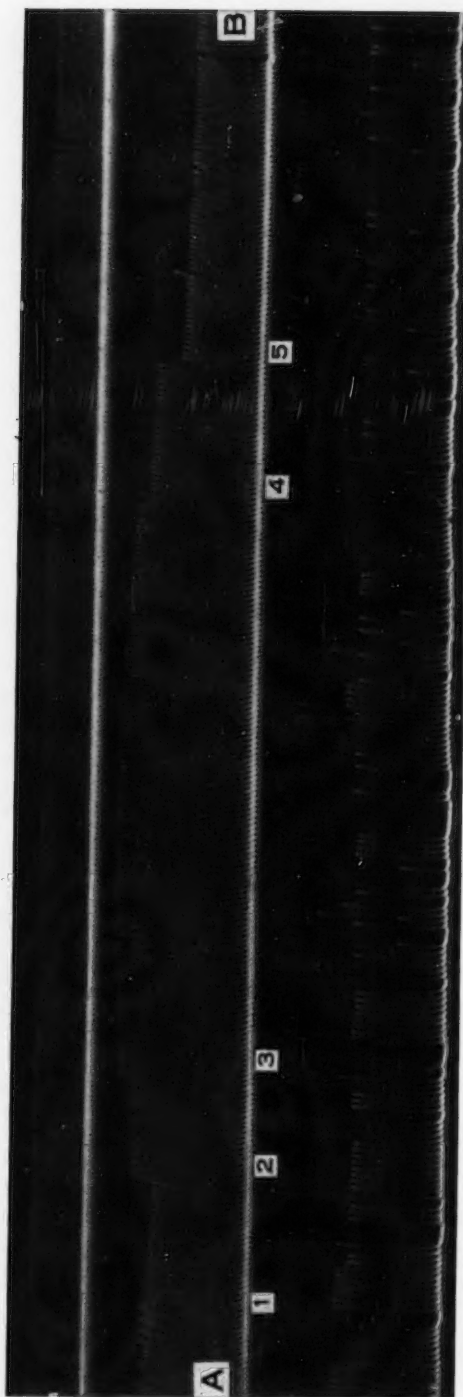


Fig. 37. Enlarged portion of the three series of figure 36, A-B. In the lower series the stimuli are sufficiently fluctuant to encroach upon several quantal thresholds. The upper series shows continuous fatigue of the dominant quantal. From A to B the chief events are as follows:

1. Continuous fatigue of dominant quantal, with initial fluctuations, probably of quantal character.
2. A higher quantal undergoing staircase increment.
3. A third quantal, with initial staircase merging into fatigue.
4. Abrupt return to the second step, but with continuity of fatigue gradient.
5. Resumption of fatigue gradient of dominant quantal.

The differential significance of this record is discussed in the text.



interpreted in terms of continuity; to what extent in terms of discontinuity? Until these precincts, which certainly appear to overlap where the tissue is studied in the gross, can be defined it is unsafe to reason from molar to molecular events.

Even staircase and fatigue effects, as already shown, may be described in strictly quantal terms. These may further be superimposed on continuous gradients in such a way that only extreme reduction to terms can separate the two distinct types of response. The tracing *A, B* in figures 36 and 37 emphasizes this very sharply. The series taken together is a staircase, merging into a fatigue. But it is quantally composed; each quantal having apparently its own state of irritability and contractility. Analysis shows that the whole is subject to the slow degradation of a dominant quantal reflecting long continued activity, carrying the others as they appear. But its dominance is utterly obscured temporarily by the idiosyncrasies of the less fatigued elements, which manifest their own gradients quite independently. A muscle capable of differential activity of this sort would indeed prove deceptive toward any attempted description.

Apparently the sufficiently complex web of muscular behavior must be approached on wholly new lines of analysis, directed toward the disentanglement of the actual from the seemingly continuous processes. It is not to be wondered, therefore, that so many phases of muscular function, though elicited with ease, have remained in their essence obscure and baffling. Such problems need restatement to yield new points of attack.

#### SUMMARY

A complete account is given of the method for photographically recording the contraction of muscle fibers on excitation with the pore-electrode. By the use of the apparatus an experimenter is enabled to watch through a demonstration ocular the movements of the recording mercury-globule-mirror on the surface of the muscle, while these are being automatically recorded, and at the same time register on the plate, by turning a lever, the actual extent of movement of a secondary coil. Thus the continuity of stimulus variation is shown in a curve coördinate with that which reveals the quantal or discontinuous character of contraction gradients.

Full details of principles and construction are shown in the drawings, and a number of graphic records are reproduced, illustrating the different phases and capabilities of the method.

On these records further and more complete evidence is based with respect to the all-or-none behavior of the skeletal muscle cell in simple contraction, tetanus, and staircase and fatigue effects; and the significance of latent periods as obtained by the method is briefly discussed.

Emphasis is laid on the opportunity for analysis of mechanical effects which the method furnishes, since the continuous gradients can thereby be readily differentiated from the discontinuous—functions which must always tend to confusion or obscurity in gross muscular action.

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## ON THE FUNCTIONAL CORRELATION OF THE HYPOPHYSIS AND THE THYROID

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### INTRODUCTION

Workers have for a long time noted certain resemblances in structure between the hypophysis and the thyroid gland. Thus there is a substance present in the pituitary which resembles the colloid material in the thyroid. Again in addition to marked similarities of function in relation to metabolic processes these two endocrine glands play an almost identical rôle in respect to growth. The extirpation of either gland slows or checks developmental processes in general, and especially interferes with the functions of the sexual organs and the nervous system.

If the extirpation of one gland causes changes in the structure and function of the other, there is ground for suspecting that there exists normally a functional reciprocity between the two. For instance, if the hypophysis should undergo hypertrophy as a result of thyroidectomy a natural inference would be that the pituitary had taken over some part, if not all, of the functions of the thyroid. Such an inference would be strengthened if one gland could be substituted for the other.

The literature upon the results of hypophysectomy is very meager owing to the inaccessibility of the gland and the difficulties encountered in its removal.

Smith (57) and Allen (1) working independently, found that hypophysectomy in frog embryos produced changes in the thyroid. The glands in most cases were only about one-third as large as those of the controls and showed atrophic conditions histologically.

Pardi (39) experimented to determine whether modifications of the structure of the thyroid could be caused by pituitary extracts or by other extracts, spleen and liver, as well. He found changes of structure which indicated colloid hypersecretion but that practically the same alterations followed the injection of the various extracts.

Cushing (15) reports in six dogs a hypertrophy of the thyroid after hypophysectomy. Blair Bell (6) states that after extirpation of the pituitary

One anticipated finding hyperplasia in the thyroid, for Cushing is very definite on this point, but in no case was any change to be discovered.

While after complete removal of the anterior lobe no changes could be seen, he found in one dog following partial extirpation of the anterior lobe that the thyroid was enlarged but normal histologically. Housay (28), in the dog, reports an excessive accumulation of colloid and sometimes degeneration of the cells in the thyroid following the removal of the hypophysis. Aschner (3) found that the extirpation of the pituitary in young animals causes increase of colloid in the thyroid.

From the above results it is apparent that hypophysectomy causes marked changes in the structure and appearance of the thyroid. On the other hand the effects of thyroidectomy upon the pituitary are even more pronounced.

Rogowitsch (49), in 1886, found enlargement of the pituitary following thyroidectomy in rabbits and dogs. He also reported an increased production of colloid by the cells of the anterior lobe with indication of its passage into the blood vessels. In rabbits he found a doubling of the weight of the hypophysis. He was induced by these results to formulate the theory that after thyroidectomy the pituitary takes over the function of the thyroid gland, and as a result of its increased activity endeavors to compensate for the loss of the thyroid secretion. In the herbivora where there is but little apparent effect of thyroidectomy the pituitary is large and the compensation is sufficient to meet the requirements, but in the carnivora the pituitary is small and the animal dies as a result of thyroid deficiency. Later the discovery of the true relationship of the parathyroids to the thyroid accounted for the different symptoms exhibited by the herbivora and carnivora. However, now, evidence began to accumulate substantiating the results of Rogowitsch.

Hofmeister (26) found hypertrophy of the hypophysis in thyroidectomized rabbits, the gland having nearly doubled its weight in the course of twelve weeks. Stieda (59) described hypertrophy of the anterior lobe brought about by an increase in the number of "Hauptzellen," with the formation of vacuoles in them. He was unable to find any changes in the chromophil cells or formation of colloids. Degener (16) found the pituitary to be three times the normal size in the rabbit one

hundred and seventy-nine days after thyroidectomy. Simpson and Hunter (56) found an increase in weight of 15 per cent in lambs and 20 per cent in the adult sheep after thyroidectomy. Gley (21) reported the normal weight of the pituitary in the rabbit as 0.02 gram. This increased to 0.10 gram at the end of a year (five times the normal), after thyroidectomy. Leonhardt (34) found an increase of one-half in the hypophysis of the rabbit after one hundred and twenty-six days. Lucien and Parisot (36) always found an increase in the weight of the hypophysis in the rabbit. Cimatori (12), in the dog and rabbit, found a distinction between the nature of the hypertrophy of the pituitary which resulted from castration and from thyroidectomy. Torri (61), in the same animals, reported similar changes. Parhon and Galstein (40) always found a hypertrophy. Traina (62) found little or no increase after fifteen days. Hoskins (27), in his experiments upon amphibia, found what he designates physiological hypertrophy of the anterior lobe of the pituitary after thyroidectomy. This explains the gigantism and infantilism noted in the thyroidless larvae. The failure to metamorphose was due either to the loss of the thyroid or to the abnormal secretion of the anterior lobe. The hypophysis of the female was larger than that of the male. This might account for the fact that the ovary differentiates earlier than the testes. Rogers (48) reports an enlargement of the anterior lobe in *Rana pipiens* following thyroidectomy. Alquier (2) saw in the dog an increase in volume and signs of hyperactivity. Kamo (30) reported a hypertrophy of the hypophysis in puppies one and a half to five months after thyroidectomy, the pituitary being enlarged to two to five times the normal size. The chief change was in the anterior lobe. An enlargement was also noted in the adult dogs after operation. He also reported that parathyroidectomy caused no changes in the anterior lobe, but an increase in volume of the pars intermedia in puppies and an augmented deposit of colloidal substance in the adult animals. Thaon (60) perceived hypertrophy and structural changes in the young ram after forty days.

Trautmann (63) studied the effects of thyroidectomy in goats and reported a hypertrophy of the pituitary. In a histological examination he detected vacuolized areas and other evidences of what he considered to be degenerative changes. Therefore the hypertrophy may be of a pathological nature and not indicative of physiological activity.

Klebs (32) found hyaline globules in the blood vessels of the nervous part of the pituitary, struma-priva dogs, and therefore assigned the origin of the disturbance to this organ.

Boyce and Beadles (9), in cases of myxedema, reported an enlargement of the pituitary and an increase of colloid in the posterior part of the anterior lobe. Large cysts filled with colloid were seen here. The posterior lobe was atrophied.

Herring (25) worked with cats, dogs and rabbits. The changes were most marked in the rabbit. He found that the anterior lobe was apparently unaffected but that there was increased activity of the cells of the pars intermedia and a probable increase in the number of these in animals surviving the operation for a considerable period. He noted that the changes were most marked in the nervous portion of the posterior lobe and in the laminae constituting the floor of the third ventricle. Here colloidal bodies of a hyaline or granular nature were very numerous. There were also localized proliferations of neuroglia. According to Herring, the extensive production of colloid was merely an exaggeration of a normal process.

Degener (16) found that the hypertrophy affected all parts but most of all the pars anterior in which sometimes colloid vesicles develop similar to those of the thyroid. Halpenny and Thompson (24) described enlargement of the pituitary with an increase of the colloid vesicles in the pars intermedia. Kojima (33) reported that in an animal killed thirty-four days after thyroidectomy the pars anterior was less compact in structure than in the normal rat, and a larger number of vesicles were visible over the whole section. These vesicles varied in size and shape. Many were filled with a hyaline substance, which stained faintly red with eosine; others were empty; there were also a number of large, swollen-looking cells, the cytoplasm of which was opened in appearance. Numerous small vacuoles were noticed. The ordinary oxyphil and basophil cells are remarkably few in number. The pars intermedia was relatively thickened. These changes were already visible twenty-three days after thyroidectomy and they were not removed after feeding the animals for some days with one gram of ox-thyroid per rat per diem.

A. E. Livingston (35) found that thyroid feeding prevented the increase in the size of the pituitary which would otherwise be caused by thyroidectomy.

Thus, to recapitulate, practically all investigators agree that the pituitary increases in size as a result of thyroidectomy and that the gland contains an increased amount of colloid material. Opinion, however, differs as to where in the gland this colloid is found. According to Simpson and Hunter, the pituitary colloid is not identical with that of the thyroid and contains no iodine or but slight traces.



On the clinical side there is also evidence of disturbances in the hypophysis as a result of thyroidectomy. Nièpee (37), in five cretins, found all the pituitaries to be enlarged. Pisenti and Viola (43) found much colloidal substance in the pituitary in cases where the thyroid was the seat of a fibrous struma. Dolega (18) reported that in a cretinoid skull the pituitary fossa was relatively larger than in the normal skull. Boyce and Beadles (9), observed hypertrophy of the gland in cases of myxedema, with increase of colloid in the posterior part of the anterior lobe, a doubling of weight. Schönemann (54), from the study of the pituitary and thyroid glands of one hundred and twelve cases in Kocher's clinic, found support for the hypothesis of Rogowitsch. Comte (13), in one hundred and eight cases of thyroid disease, found a hypertrophy of the hypophysis when the thyroid showed atrophic changes. Calderara (10) reported the same in a case of myxedema and the presence of much colloid in the pituitary. Bourneville and Bricon (8) found enlargement of the pituitary in cretins. Eichorst (19) found in cretins and cases of myxedema a hyperfunction of the pituitary. The gland was larger and hyperemic. There were often hemorrhages and later a growth of connective tissue and cyst formation. Finally the pituitary became smaller and smaller. Wells (64), in a case of scleroderma where the thyroid was greatly atrophied, found the hypophysis to be twice the normal size and this increase seemed to be due to the large accumulation of colloid material.

On the other hand, in some cases, no change in structure could be detected and in a few cases the pituitary was below normal. Coulon (14), in five cretins, found the pituitary to be normal or below the average size. Ponfick (45), in a case of myxedema, found a degeneration of the pituitary.

Thus the preponderance of clinical evidence points to hypertrophy of the hypophysis as a result of thyroid deficiency.

Simpson and Hunter (56) experimented on the assumption that the iodine-containing body in the thyroid represents the active principle or internal secretion of the gland. Therefore if there were a compensatory activity on the part of the pituitary as a result of thyroidectomy they expected to find some iodine. The failure to detect iodine is considered as evidence against the theory. They found in the sheep that removal of the thyroid does not lead to the appearance of iodine in the pituitary and that therefore there is no vicarious relationship between the two glands. Their assumption is based on the statements of Baumann (5), Halliburton, Candler and Sikes (23), that there is no iodine

in the human pituitary. On the other hand Schnitzler (53) did find positive evidence of iodine in the human pituitary but in very small amount. He therefore assumed that the iodine is present as iodothylin and brings forward his result in support of the view that the thyroid and pituitary may act vicariously. Wells (64) also found a small amount of iodine in the human pituitary. As compared with the thyroid the proportion was about 1:50. Pellegrini (41) studied the relation of the thyroid iodine to pituitary functioning. According to the abstract (the original was not accessible to me),—

No relation was discovered between the volume of the hypophysis and the amount of thyroid iodine. The same is true as regards microscopic evidence of functional activity, relative size of the lobes of the hypophysis or frequency of occurrence of the various cellular elements. There was noted a marked lack of pigment in the neural lobe in cases in which the iodine was decreased.

The failure of Simpson and Hunter to detect iodine in the pituitary after thyroidectomy does not necessarily invalidate the idea of a functional correlation. The autacoid supplied by the hypophysis although perhaps not containing iodine may be able partially or wholly to take the place of the thyroid hormone.

In addition to the experimental data it may be mentioned that considerable clinical evidence exists of the correlations between the two glands. Thus Falta (20, p. 323) calls attention to the fact that after extirpation of a part of an adenoma in a case of acromegaly, there was an enlargement of the thyroid. Again, Benda (7) is quoted as saying that in Basedow's disease the glandular hypophysis is small. Josefson (29) reported associated hyperplasia of the hypophysis in a case of congenital struma of the thyroid.

It is interesting to note that pathological processes may occur spontaneously in the two ductless glands. To illustrate, Rosenhaupt (50) reported a case of sarcoma of the anterior lobe of the hypophysis, in which there was also a tumor of the same nature in the thyroid gland. Again indications of hyperthyrosis may occur with corresponding pathologico-anatomical alterations of the thyroid gland. In multiple ductless glandular sclerosis the sclerotic process usually affects the hypophysis and the thyroid. A slight degree of thyroid gland insufficiency may occur in hypophyseal dystrophy. Also the hypophysis may degenerate in the later stages of Basedow's disease. Again Falta (20) states

The pathologico-anatomical finding in the thyroid gland in acromegaly almost always shows something abnormal. When hyperthyrosis has existed, there is found the picture of a Basedow's struma. Otherwise there is seen almost always connective tissue proliferation, such as is found also in other organs in acromegaly, or colloid degeneration in combination with, eventually, high-grade sclerosing and atrophy of the parenchyma. Gaussel found a thyroid gland that was normal.

Thus a summary of the literature clearly establishes the fact that the removal of either the hypophysis or the thyroid gland causes definite changes in the structure of the other.

In the case of thyroidectomy the consensus of opinion is that the hypophysis undergoes hypertrophy. As to which portion enlarges the most, the anterior lobe is indicated wherever a specific region is mentioned. In making any statement, however, regarding hypertrophy of the pituitary, the extreme variations normally occurring in animals of the same species and of the same size must be taken into consideration. For instance, some of the glands of the ox often exhibit two or three times the proportions found in others. This fluctuation merely emphasizes the necessity for accurately controlled investigation.

Hypertrophy of the hypophysis following thyroidectomy has by many investigators been considered evidence of a vicarious relationship between the two glands. Assuming that the hypertrophy of the hypophysis is physiological, the next question to arise is that of the extent to which the pituitary can function for the thyroid. That the substitution, if it exists, is incomplete may be shown by the myxedematous symptoms and often the death of the animal following thyroidectomy. Since the compensatory effort on the part of the pituitary substance attempting to perform a double function in the absence of the thyroid is insufficient, the administration of hypophyseal extract should prove beneficial. Through the adjuvant action of the added hormone the pituitary might now perform its double task.

#### THE EFFECT OF ADMINISTRATION OF THE ANTERIOR LOBE OF THE HYPOPHYSIS TO THYROIDECTOMIZED RATS

In order to ascertain the effects of direct administration of the anterior lobe to thyroidectomized animals it was essential to find a species in which the injurious effects of parathyroidectomy were at a minimum. It is usually impossible to extirpate the thyroids completely without injury to the parathyroids.

The rat was finally chosen, as this animal is particularly favorable for these experiments and is not subject to tetany as an early result of removal of the parathyroid. The only apparent modifying factor is that of age. I have found that rats weighing less than forty grams invariably die as the result of operation, convulsions being observed in some cases.

The rats selected were approximately of the same size, age and strain, and wherever possible, from the same litter. The importance of these details in the selection of controls cannot be over-estimated. Growth curves of normals obtained in one can not properly be compared with those of experimental animals at another season. The thyroids and parathyroids were completely removed under ether anesthesia. After some preliminary operation work to ascertain the simplest technique and the most favorable age, the rats were divided into four groups. Two series were operated and fed fresh liver and anterior lobe of the ox respectively in addition to the normal diet. Two other groups were control animals and fed liver and anterior lobe; the amount of liver administered corresponded to the quantity of hypophysis substance.

The rats were all kept in individual cages in order to insure a uniform consumption of the glandular food. An excess of food was furnished so that the rats had access to as much as desired. The ordinary diet consisted of swill, barley, cooked rice and fresh cabbage, but no water as the animals seemed to thrive best without it. Besides the special glandular materials, a small quantity of salt was kept in each cage. As for the dosage of anterior lobe administered, the average amount during the first three months varied from one-half to one gland per rat, and later, two to three glands administered at least three times a week and more frequently when the glands could be obtained. But in every case the same amount was fed to each rat of the two series. The dosage used is larger than that usually reported as allowance was made for a destruction of some of the active principle in its passage through the alimentary tract before absorption.

In an attempt to determine the maximum amount of glandular substance utilized, all of the excess of glands after each feeding was administered to two individuals, one in each of the pituitary groups. The number of glands varied from two to eighteen per rat, but each received the same amount. In comparison with their respective groups the operated rat thrived best, the normal individual losing weight, but no more than a rat fed the ordinary amount. These results seemed to

indicate that the organism is capable of utilizing only a certain amount of the pituitary autacoids, and that an excess is eliminated without any deleterious effects.

The hypophyseal substance was given to the animal in a separate dish and from the outset the rats exhibited a marked predilection for the anterior lobes, eating with great avidity all that was administered. After two or three feedings the animals would snatch the glands out of the dishes in preference to any other food. In fact the glands were consumed with greater eagerness than the liver in the other groups.

The rats were weighed each week and their general condition noted. When an animal died a careful search was made for thyroid tissue. Any rats dying less than two weeks after the operation or from known accidental causes were discarded. The experiment proper commenced June 3, 1918, and terminated February 3, 1919. The remaining rats were killed and prepared for subsequent examination.

The entire group of rats, seventy in number, was subdivided into the four series. The subsequent history of each rat was recorded in tabular form, the data being secured from the record of weekly weighings and curves plotted from the same. Two distinct sets of tables were drawn up, the first of which, tables 1 to 4, commence the experiment with the initial weighing of each rat. The chief value of the results presented herein is to indicate the conditions of growth before operation. It was found that thyroidectomy caused but slight immediate effect; in some cases a loss of a few grams was noted at the time of the next weighing.

In the second set, tables 5 to 14, the same data are used but the comparisons begin with the date of operation. The results stated in this form are seen to emphasize the relations observed in the first set of protocols. Upon comparing the two sets the chief difference is to be found in the figures which are based on the weight changes, although the relative proportions of the different groups remain unchanged. Since the date of operation marks the true beginning of the experiment, the second set of tabulations will be more particularly considered.

In all of the tables, the sign X indicates that the animal died; the sign + shows that the animal is still living; the sign  $\phi$  denotes death due to accident; 2/3 is the date of termination of the experiment.

The foregoing tables present the data in one comparative way, but as stated above certain facts are brought out more clearly by a different arrangement. In the following tables the comparison begins with the date of operation and a corresponding day for the unoperated animals.

TABLE 1

*Control. Ordinary dietary with the addition of liver*

GROUP NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
			grams	grams	days
X A 25					
A 50	♀	6/4 to 1/20	201 to 246	+45	230
A 1	♀	6/3 to 2/3	184 to 180	-4	245+
A 46	♀	6/3 to 2/3	232 to 235	+3	245+
A 3	♀	6/4 to 2/3	211 to 233	+22	244+
A 28	♀	6/4 to 2/3	189 to 203	+14	244+
A 4	♀	6/4 to 2/3	250 to 174	-76	244+
A 20	♂	6/27 to 2/3	189 to 300	+111	221+
D 15	♀	8/26 to 2/3	76 to 158	+82	162+
E 34	♀	8/26 to 2/3	65.5 to 186	+120.5	162+
G 2	♂	7/8 to 2/3	20 to 173	+153	210+
G 71	♀	7/8 to 2/3	22 to 164	+142	210+
J 12	♀	6/27 to 2/3	35 to 103	+68	221+
J 90	♂	6/27 to 2/3	36 to 194	+158	221+

Total number of rats = 14. Average gain = 64.5 grams. Total number of rats dead (one was accidental) = 2. Average percentage of deaths = 7.6 per cent. Average duration of experimental life = 219.9 days.

TABLE 2

*Control. Ordinary diet with the addition of anterior lobe*

GROUP NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
			grams	grams	days
A 11	♀	6/27 to 2/3	281 to 276	-5	221+
A 18	♀	6/27 to 2/3	288 to 336	+48	221+
A 19	♂	6/4 to 2/3	247 to 304	+57	244+
A 10	♂	6/4 to 2/3	263 to 288	+25	244+
A 82	♀	6/4 to 2/3	240 to 227	-13	244+
C 16	♀	6/27 to 2/3	48 to 255	+207	221+
C 57	♀	6/27 to 2/3	48 to 233	+175	221+
E 87	♂	8/26 to 2/3	49.5 to 154	+104.5	162+
E 16	♂	8/26 to 2/3	63.5 to 199	+135.5	162+
F 73	♀	8/7 to 2/3	36 to 206	+170	181+
G 13	♂	8/7 to 2/3	20 to 159	+139	181+
G 57	♀	8/7 to 2/3	21.9 to 128	+106.1	181+

Total number of rats = 12. Average gain in weight = 95.7 grams. Total number of rats dead = 0. Average duration of experimental life, 206.9 days. Percentage of deaths = 0 per cent.



Altogether there are ten distinct groups (A to J inclusive), these being arranged according to age, litters, etc. Group A contains thirty individuals, seventeen of which, after a month of study (in nearly every case, see tables 3 and 4) were operated the first week in July. The legends at the heads of the tables are self-explanatory, the X at the left

TABLE 3  
*Thyroidectomized rats fed upon the ordinary diet and liver*

GROUP NUMBER	SEX	DURATION OF EXPERIMENT	DATE OF OPERATION	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
				grams	grams	days
φ A 9	♀	6/4 to 2/3	6/24			
φ A 8	♀	6/12 to 2/3	6/21	230 to 205	-25	235+
X A 6	♀	7/3 to 11 8	7/6	235 to 238	+3	128
X A 4	♀	7/8 to 10/15	7/8	157 to 127	-30	99
X A 91	♂	7/5 to 10/20	7/13	51 to 202	+51	107
X A 7	♀	6/4 to 10/7	6/20	216 to 125	-91	125
X A 17	♀	6/4 to 12/2	7/21	261 to 189	-72	181
X A 8	♀	6/27 to 8/28	6/28	105 to 84	-21	63
X A 22	♀	6/29 to 8/20	7/16	23 to 54.5	+31.5	52
X A 33	♂	7/13 to 9/26	9/13	17 to 51	+34	75
X A 39	♂	8/14 to 9/4	8/15	73 to 85	+12	21
X D 88	♀	8/26 to 12/2	9/12	46 to 120	+74	98
X D 14	♀	8/26 to 10/4	9/12	46 to 56	+10	39
φ E 6	♀	8/26 to 9/14	9/13	60.5 to 89	+28.5	19
X E 56	♀	8/26 to 11/18	9/12	45.5 to 76	+30.5	84
φ H 27	♂	8/6 to 1/20	8/9	99 to 316	+217	166
H 32	♂	8/7 to 2/3	8/9	79 to 315	+236	179+
X H 80	♂	8/8 to 8/30	8/9	67.5 to 90	+22.5	22
X I 43	♀	8/1 to 12/22	9/19	21 to 89	+68	143
I 45	♂	7/13 to 2/3	9/20	14 to 189	+175	204+
X G 5	♀	6/27 to 9/26	7/18	27 to 77	+50	91

Total number of rats = 21. Total number of rats dead = 18. (Three accidental deaths). Total number of rats alive = 3. Percentage of deaths = 78.9 per cent. Average gain in weight = 40.8 grams. Average duration of experimental life = 111.1 days.

signifying a death presumably due to experimental conditions or to unknown causes in the controls. The φ connotes either an accidental death, doubtless due to shock, etc., as most of these deaths occurred the day following the operation, or to the escape of the animal. The date 2/3 indicates that the individual is still living.

Table 5 represents the histories of eight rats. The dates 6/28 and 7/3, were taken as the initial date to correspond with the operative dates. Of the eight individuals there were two deaths, one accidental. The average duration of life of the entire group is 207.8 days. The sign + in last column indicates that the animals are still living. The total

TABLE 4  
*Thyroidectomized rats fed upon the ordinary diet and anterior lobe*

GROUP NUMBER	SEX	DURATION OF EXPERIMENT	DATE OF OPERATION	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERI- MENTAL LIFE
				grams	grams	days
A 35	♂	6/12 to 2/3	6/25	165 to 161	-4	235+
A 13	♀	6/3 to 2/3	7/3	98 to 130	+42	245+
A 58	♀	6/3 to 2/3	7/3	157 to 199	+42	245+
A 14	♂	6/4 to 2/3	6/18	87 to 250	+163	244+
X A 81	♀	7/6 to 12/22	7/6	208 to 293	+85	169
X A 12	♀	6/27 to 11/30	6/28	197 to 170	-27	156
X B 11	♀	6/4 to 10/7	6/25	71 to 133	+62	125
B 51	♀	6/4 to 2/3	6/20	67 to 229	+162	244+
B 15	♂	6/4 to 2/3	6/25	50 to 276	+226	244+
D 89	♀	8/25 to 2/3	9/13	56 to 104	+48	16+
♂ D 30	♂	8/26 to 9/22	9/21	61 to 89	+28	.
X E 18	♀	8/26 to 11/16	8/29	67.5 to 116	+48.5	82
X E 2	♀	8/26 to 10/25	9/13	56 to 104	+48	60
H 17	♀	8/7 to 2/3	8/9	64 to 196	+132	181+
H 78	♂	8/8 to 2/3	8/9	104 to 134	+30	180+
H 79	♂	8/8 to 2/3	8/9	97 to 327	+230	180+
X H 44	♂	8/7 to 10/16	8/7	70 to 85	+15	60
X I 3	♀	7/5 to 12/3	7/10	35 to 104	+69	151
I 24	♂	6/29 to 2/3	7/26	29 to 279	+250	219+
I 31	♀	7/5 to 2/3	7/10	49 to 234	+185	213+
♂ J 70	♀	8/8 to 11/12	8/12 escaped			25

Total number of rats = 21. Average gain in weight = 105.3 grams. Total number of rats dead = 9; (two accidental). Average duration of experimental life = 179.5 days. Average percentage of deaths = 37.5 per cent. Total number of rats alive = 12.

gains in weight are 179 grams and the total losses are 185 grams, making the average 0.75 gram.

Table 6 shows the effect of the addition of the anterior lobe to the dietary of the rats. There were no deaths, the average duration of life was 218.6+ days. The average gain for the group is +27 grams.

TABLE 5

*Group A. Control, fed upon normal diet and liver*

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
			grams	grams	days
X A 25	♀	6/28 to 12/1	276 to 183	-93	155
A 50	♀	7/3 to 1/20	218 to 246	+28	221+
A 1	♀	6/27 to 2/3	175 to 180	+5	221+
A 46	♀	6/27 to 2/3	220 to 235	+15	221+
A 3	♀	6/27 to 2/3	232 to 233	+11	221+
A 28	♀	7/3 to 2/3	187 to 203	+16	215+
A 4	♀	7/3 to 2/3	266 to 174	-92	215+
A 20	♂	7/3 to 2/3	196 to 300	+104	215+

TABLE 6

*Group A<sub>2</sub>. Control, fed upon usual diet and anterior lobe*

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
			grams	grams	days
A 11	♀	6/27 to 2/3	280 to 276	-4	221+
A 18	♀	6/27 to 2/3	288 to 336	+48	221+
A 19	♂	6/27 to 2/3	265 to 304	+39	221+
A 10	♂	7/3 to 2/3	255 to 288	+33	215+
A 82	♀	7/3 to 2/3	208 to 227	+19	215+

TABLE 7

*Group A<sub>3</sub>. Thyroidectomized rats fed upon normal diet and liver*

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
			grams	grams	days
φ A 9	♀	6/24 to 2/3	222 to 238	+16	
A 8	♀	6/21 to 2/3	207 to 205	-2	227+
X A 6	♀	7/6 to 11/8	232 to 238	+6	125
X A 4	♀	7/8 to 10/15	165 to 127	-38	99
X A 91	♂	7/13 to 10/20	81 to 102	+21	99
X A 7	♀	6/20 to 10/7	235 to 125	-110	109
X A 17	♀	7/2 to 12/2	265 to 189	-76	153
X A 8	♀	6/28 to 8/28	105 to 84	-21	61
X A 22	♀	7/16 to 8/20	48 to 54.5	+6.5	35
X A 33	♂	9/13 to 9/26	55 to 51	-4	13
X A 39	♂	8/15 to 9/4	73 to 85	+12	20

Group A<sub>3</sub>, table 7, shows nine deaths out of ten operated animals, the average life after operation being 71.4 days, and of the group, 94 days. The sign + means that one rat is still living. Thus there is 90 per cent of deaths, an average gain of -20.5 (obtained by adding the gains and losses algebraically and dividing by the number of individuals). Of the rats which died, four showed myxedematous symptoms—rats A 6, A 4, A 7 and A 8.

On the other hand group A<sub>4</sub>, table 8, exhibits 33.33 per cent of deaths and an average duration of life of 201.1 days for the group, that for the two dead being 162 days.

TABLE 8

*Group A<sub>4</sub>. Thyroidectomized rats fed upon normal diet and anterior lobe*

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
			grams	grams	days
A 35	♂	6/25 to 2/3	175 to 161	-14	223+
A 13	♀	7/3 to 2/3	128 to 130	+2	215+
A 58	♀	7/3 to 2/3	163 to 199	+36	215+
A 14	♂	6/18 to 2/3	87 to 250	+163	230+
X A 81	♀	7/6 to 12/22	208 to 293	+85	169
X A 12	♀	6/28 to 11/30	205 to 170	-35	155

TABLE 9

*Group B. One litter. Thyroidectomized rats fed upon normal diet and anterior lobe*

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
			grams	grams	days
X B 11	♀	6/25 to 10/7	93 to 133	+40	104
B 55	♀	6/20 to 2/3	103 to 229	+126	228+
B 15	♂	6/26 to 2/3	75 to 276	+201	223+

Whereas from the previous group there is but one rat alive, here there are four. The average gain is 39.5 grams. A 81 seemed hyper-irritable, very nervous and maintained its head tilted to one side.

In B, table 9, another operated group to which the hypophysis was added, one death occurred, with an average duration of life for the group of 185 days and an average gain of 122.3 grams.

In C, table 10, there is an average life of 221+ days and gain of 191 grams.

In groups D and E, tables 11 and 12, 9/12 is taken as the start of the experiment for the normals to correspond with that of the operated animals.

The average life in D was 144 days for the normal; 51.5 days for the operated + liver; and 143+ days for the operated + pituitary; while the average gains were +95, +12.5 and +103; the per cent deaths, 0 per cent; 100 per cent and 0 per cent.

TABLE 10

*Group C. One litter. Control fed upon normal diet and anterior lobe*

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
			grams	grams	days
C 16	♀	6/27 to 2/3	48 to 255	+207	221+
C 57	♀	6/27 to 2/3	48 to 223	+175	221+

TABLE 11

*Group D. One litter*

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
<i>Group D. Control, fed upon normal diet and liver</i>					
			grams	grams	days
D 15	♀	9/12 to 2/3	84 to 179	+95	144+
<i>Group D. Thyroidectomized, fed upon liver and normal diet</i>					
X D 88	♀	9/12 to 12/2	80 to 120	+40	81
X D 14	♀	9/12 to 10/4	71 to 56	-15	22
<i>Group D. Thyroidectomized, fed upon anterior lobe and normal diet</i>					
D 89	♀	9/13 to 2/3	56 to 159	+103	143+
φ D 30	♂	9/21 to 9/22			1

In the above litter the percentages of death were: 0.0 per cent; 0.0 per cent; 100 per cent and 100 per cent respectively; and the average life 144+ days; 144+ days; 67 days and 68 days, while the average gains were +78 grams; +82 grams; +9 grams and +76 grams. This lot presents the first and only instance where the life of a thyroidectomized and liver-fed animal after operation is nearly equal to that of the pituitary series. The condition of growth in these two series may

be compared by examining the group gain, which is +9 grams in the liver series and +76.5 grams in the pituitary individuals. In this as in the preceding families, the maximum duration of life is 144+ days in the controls, as the experiment commenced September 12.

The preceding set is largely composed of normal individuals. The average life is 180+ days in the pituitary-fed series and the corresponding ones in the other series. If there is any difference in the rate of growth, the figures favor the pituitary rats.

TABLE 12  
*Group E. One litter*

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
1 Rat. Control, fed upon liver and normal diet					
E 34	♀	9/12 to 2/3	grams 108 to 186	grams +78	days 144+
Group E. Control, fed upon anterior lobe added to normal diet					
E 87	♂	9/12 to 2/3	92 to 154	+62	144+
E 16	♂	9/12 to 2/3	97 to 199	+102	144+
Group E. Thyroidectomized rats fed upon normal diet with liver					
φ E 6	♀	9/13 to 9/14			1
X E 56	♀	9/12 to 11/18	67 to 76	+9	67
Group E. Thyroidectomized rats fed upon normal diet with anterior lobe added					
X E 18	♀	8/29 to 11/16	67.5 to 116	+48.5	79
X E 2	♀	8/29 to 10/25	72.5 to 176	+103.5	57

The life of the normals in J is 200+ days as contrasted with 70 days in the control operated rodent, and 92 days (before its disappearance) in J 70, the pituitary-fed individual.

Upon making deductions from the above group, H 27 is regarded as living since the animal was killed near the termination of the experiment in attempt to ascertain how much thyroid material was present; no thyroid substance was found. There was one death after 20 days in the first group as opposed to one after 61 days in the pituitary animals. The average gain was 158.5 grams as compared with 101.8 grams although the average duration of life was 121+ days in comparison with 148.7+ days.



TABLE 13

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
Group F. Control, fed upon anterior lobe added to normal diet					
F 73	♀	8/7 to 2/3	grams 36 to 206	grams +170	days 180+
Group G <sub>2</sub> . Control, fed upon liver added to normal diet					
G 2	♂	8/7 to 2/3	53 to 173	+120	180+
G 71	♀	8/7 to 2/3	65 to 174	+109	180+
Group G. Control, fed upon pituitary added to normal diet					
G 13	♂	8/7 to 2/3	20 to 159	+139	180+
G 57	♀	8/7 to 2/3	21.9 to 128	+106.1	180+
Group J (one litter). Control, liver added to usual diet					
J 12	♀	7/18 to 2/3	55.5 to 108	+47.5	200+
J 90	♂	7/18 to 2/3	59.5 to 194	+134.5	200+
Group J. Thyroidectomized rat fed with liver added to usual diet					
X J 5	♀	7/18 to 9/26	46 to 77	+31	70
Group J. Thyroidectomized rat fed with pituitary added to usual diet					
ø J 70	♀	7/14 to 10/14	(escaped)		92

TABLE 14

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
Group H. Thyroidectomized rats, fed with usual diet and liver					
ø H 27	♂	8/9 to 1/20	grams 99 to 316	grams +217	days 165
H 32	♂	8/9 to 2/3	79 to 315	+236	178+
X H 80	♂	8/9 to 8/29	67.5 to 90	+22.5	20
Thyroidectomized rats fed with usual diet with addition of anterior lobe					
H 17	♀	8/9 to 2/3	64 to 196	+132	178+
H 78	♂	8/9 to 2/3	104 to 134	+30	178+
H 79	♂	8/9 to 2/3	97 to 327	+230	178+
X H 44	♂	8/6 to 10/6	70 to 85	+15	61

Ignoring the two deaths in the first group, which were possibly due to tetany or some operative factor, there is one death 94 days after operation as compared with one after 146 days in the second series. The average duration of life of the groups is 113.5+ days and 182+ days. This despite the fact that the animals in the latter lot were operated two months prior to that of the first and at that time were younger and therefore less liable to live. The average gains were 51.3 grams and 161.3 grams. An individual analysis of each group therefore reveals the fact that the life is longer and the growth is greater in the pituitary fed operated rats.

TABLE 15

NUMBER	SEX	DURATION OF EXPERIMENT	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
Group I. Thyroidectomized rats fed upon usual diet to which liver was added					
XI 43	♀	9/19 to 12/22	grams 81 to 89	grams +8	days 94
I 45	♂	9/20 to 2/3	94.5 to 189	+94.5	133+
♂ I 47		10/10 to 10/11			1
♂ I 13		9/13 to 9/14			1
Group I. Thyroidectomized rats fed upon usual diet to which anterior lobe was added					
X I 3	♀	7/10 to 12/3	35 to 104	+69	146
I 24	♂	7/26 to 2/3	49.2 to 279	+229.8	192+
I 31	♀	7/10 to 2/3	49 to 234	+185	208+

A critical survey of the general welfare of the living rats at the termination of the experiment disclosed the following data: In respect to nutritive condition and the appearance of their coats the rats of the liver-fed controls were decidedly inferior to those of the pituitary-fed rodents. An individual scrutiny of the various groups revealed four emaciated rats with dirty, scrawny coats among twelve normal liver-fed individuals, as compared with one emaciated rat among three operated liver-fed animals, three emaciated rats among twelve operated pituitary-fed members, while the twelve normal pituitary-fed rats were in excellent condition.

It will, perhaps, be still more instructive to exhibit the results as expressed in the form of tabular summaries. First, for the sake of convenience the histories of all the rats are recorded in one table 16.

TABLE 16A

*Normal rats fed upon normal diet with addition of liver*

NUMBER	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
	grams	grams	days
X A 25	276 to 183	-93	155
φ A 50	218 to 246	+28	200
A 1	175 to 180	+5	221+
A 46	220 to 235	+15	221+
A 3	222 to 233	+11	221+
A 28	187 to 203	+16	215+
A 4	266 to 174	-92	215+
A 20	196 to 300	+104	215+
D 15	84 to 179	+95	144+
E 34	108 to 186	+78	144+
G 2	53 to 173	+120	180+
G 71	65 to 174	+109	180+
J 12	55.5 to 103	+47.5	200+
J 90	59.5 to 194	+134.5	200+

Total = 14. Dead = 2 (1 accidental)

TABLE 16B

*Normal rats fed upon hypophysis added to normal diet*

NUMBER	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
	grams	grams	days
A 11	280 to 276	-4	221+
A 18	288 to 236	+48	221+
A 19	265 to 304	+39	221+
A 10	255 to 288	+33	215+
A 82	208 to 227	+19	215+
C 16	48 to 255	+207	221+
C 57	48 to 223	+175	221+
E 87	92 to 154	+62	144+
E 16	97 to 199	+102	144+
F 73	36 to 206	+170	180+
G 13	20 to 159	+139	180+
G 57	21.9 to 128	+106.1	180+

Total = 12. None dead

Table 17 shows the percentage of deaths in each series. In tables 5 to 16, as in the following tables, the final results are so arranged that the groups may be compared with each other in the form of group averages. Here the total average is obtained by adding the group averages and dividing by the number of component groups. But since the constituent groups differ in number this total average figure, whether

TABLE 16C

*Thyroidectomized rats fed upon normal diet with addition of liver*

NUMBER	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
	<i>grams</i>	<i>grams</i>	<i>days</i>
φ A 9	222 to 238	+16	227
A 8	207 to 205	-2	227+
X A 6	232 to 238	+6	125
X A 4	165 to 127	-38	99
X A 91	81 to 102	+21	99
X A 7	235 to 125	-110	109
X A 17	265 to 189	-76	153
X A 8	105 to 84	-21	61
X A 22	48 to 54.5	+6.5	35
X A 33	55 to 51	-4	13
X A 39	73 to 85	+12	20
X D 88	80 to 120	+40	81
X D 14	71 to 56	-15	22
φ E 6			1
X E 56	67 to 76	+9	67
φ H 27	99 to 316	+217	165
H 32	79 to 315	+236	178+
X H 80	67.5 to 90	+22.5	20
X I 43	81 to 89	+8	94
I 45	94.5 to 189	+94.5	133+
φ I 77			1
φ I 13			1
X J 5	46 to 77	+31	70

Total 23. Dead 20 (5 accidental)

representing percentages or gains in weight, is not as significant as it would be if the groups were strictly comparable in respect to size. To obviate this discrepancy in size another figure is calculated by considering all the rats in each series as members of one common family. To secure this relation each individual change is considered and the total sum divided by the number of members. The use of this result makes

the different series more directly comparable. This procedure intensifies instead of weakening the relations as found by group comparisons. Both results are recorded in the tables but the emphasis will be placed upon the figure in which all of the rats in a series are considered as belonging to one lot, prefixed in the tables by the sign\*+, whereas the sign  $\phi$  precedes the other.

TABLE 16D

*Thyroidectomized: fed upon normal diet with addition of anterior lobe*

NUMBER	INITIAL AND TERMINAL WEIGHT	GAIN OR LOSS	DURATION OF EXPERIMENTAL LIFE
	grams	grams	days
A 35	175 to 161	-14	223+
A 13	128 to 130	+2	215+
A 58	163 to 199	+36	215+
A 14	87 to 250	+163	230+
X A 81	208 to 293	+85	169
X A 12	205 to 170	-35	155
X B 11	93 to 133	+40	104
B 55	103 to 229	+126	228+
B 15	75 to 276	+201	223+
D 89	56 to 159	+103	148+
$\phi$ D 30			1
X E 18	67.5 to 116	+48.5	79
X E 2	72.5 to 176	+103.5	57
H 17	64 to 196	+132	178+
H 78	104 to 134	+ 30	178+
H 79	97 to 327	+230	178+
X H 44	70 to 85	+15	61
X I 3	35 to 104	+69	146
I 24	49.2 to 279	+229.8	192
I 31	49 to 234	+185	208+
$\phi$ J 70			70

Total number of rats = 21; number dead = 9 (2 accidental)

Table 17 shows the average percentage of deaths to be 7.6 per cent; 0 per cent, 78.9 per cent and 36.8 per cent for the respective series.

It is interesting to note that although there were nineteen rats in each of the thyroidectomized groups at the time of operation, ignoring the accidental deaths, the present number is three as compared with twelve (see table 18).

An inspection of table 19 shows that the average life of the operated individuals from the date of operation to the termination of the experiment or the death of the animal is 93.5 days in the liver-fed series, and 174.8 days in the pituitary-fed.

TABLE 17  
*Percentage of deaths in different groups*

GROUP	NORMAL	NORMAL PLUS PITUITARY	THYROIDEC- TOMIZED	THYROIDEC- TOMIZED PLUS PITUITARY
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
A.....	14.2	0	90.0	33.0
B.....				33.3
C.....		0		
D.....	0		100.0	
E.....	0	0	100.0	100.0
F.....		0		
G.....	0	0		
H.....			33.3	25.0
I.....			50.0	33.3
J.....	0		100.0	
0 Average percentage of deaths.....	2.84	0	78.8	37.5
+ Average percentage of deaths.....	7.6	0	78.9	36.8

TABLE 18  
*Numerical distribution and fate of the rats*

	NORMAL	NORMAL PLUS ANTERIOR LOBE	THYROIDEC- TOMIZED	THYROIDEC- TOMIZED PLUS ANTERIOR LOBE
Total number.....	14	12	23	21
Total number dead.....	2	0	20	9
Total number accidental deaths.....	1	0	5	2
Total number other deaths.....	1	0	15	7
Total number alive.....	12	12	3	12

While the above figures refer to the average duration of life after operation of all of the animals, whether living or dead, a consideration of tables 16C and 16D shows that of the thyroidectomized animals which died, those of the pituitary series lived the longest, 110 days as compared with 71 days.



In the above table the individuals in each series are regarded as members of one group. Since the figures obtained by considering the individual group averages are almost identical with those in the table, they are not given here. In comparing the figures representing the duration of life of the thyroidectomized animals although there is a marked difference in favor of the pituitary animals, it is of added importance to understand the connotation of the symbol +, table 19C. In the one group it indicates that the possibility of future life and maintenance is determined by the fat of three rats, (see table 18) while there are twelve members in the other group. Any speculation as to the probable duration of life of these animals will be in favor of the pitui-

TABLE 19  
*Duration of life (average); counting from the date of operation*

NORMAL	NORMAL PLUS ANTERIOR LOBE	THYROIDECTOMIZED AND LIVER	THYROIDECTOMIZED AND ANTERIOR LOBE
A. Duration of life of all individuals from the time of operation to death or the termination of the experiment			
<i>days</i> 193.5	<i>days</i> 196.9	<i>days</i> 93.5	<i>days</i> 174.8
B. Duration of life of the animals which died during the experiment			
175.5		71	110
C. Duration of life of the individuals which lived throughout the entire experiment			
196.4	196.9+	179.3+	200.8+

tary-fed individuals, as shown from the previous histories of the two groups. If the figures, obtained by considering the rats as members of the same or different groups, be compared, but very little difference can be noticed and this is of slight significance.

An idea of some of the rates of growth may be gained from table 20 which is computed by a consideration of the gains and losses before the occurrence of death or the termination of the experiment. The figures representing the liver-fed rats, normal and operated, show the least gain, while those of the pituitary-fed animals are more than doubled, in both the normal and the operated series. The lowest gain is in the operated-liver series, and the highest is in the operated-pituitary group,

but this is practically equivalent to that observed in the normal pituitary series. The results obtained from a study of individual groups, lowest line of table, exhibit the same relative differences, although the weights are higher in each case since individual deviations assume a greater value.

In answer to the possible objection that these differences might well be due to corresponding differences in weight of the animals at the outset, it will be of value to examine the initial and final records of the animals. There is, also, the objection that the higher mortality in the operated-liver series might be due to the use of younger animals, in which the effects of operation would be the most severe. But inspection of the tables shows the difference between the operated animals, only 13 grams, to be in favor of the operated-liver animals, as they were heavier at the time of operation, 113 grams in their case and 100.0 in the other. But the difference is not enough to be significant either

TABLE 20

*Average gain in weight in grams. The comparisons include the interval between the date of operation and the termination of the experiment*

NORMAL	NORMAL PLUS ANTERIOR LOBE	THYROIDECTOMIZED	THYROIDECTOMIZED PLUS ANTERIOR LOBE
<i>grams</i>	<i>grams</i>	<i>grams</i>	<i>grams</i>
+41.2	91.0	33.7	92.1
0 75.4	118.4	40.3	106.4

way. Neither is the difference between any of the weights sufficient to account for the marked deviation in the final weights; 156.1 to 197.3 and 113.0 to 136.3 in the liver-fed series and 138.3 to 230.4 and 100 to 192.1 in those animals which were fed with pituitary.

In the normal animals the difference of initial weights, 17.8 grams in favor of the pituitary-fed animals and not the liver series. Although this difference of 17.8 grams is too insignificant to account for the great deviation between the terminal weights of the liver and pituitary series, tables 1 and 2 show the weights before the administration of any liver or hypophyseal substance. Before the administration of the hypophysis the initial weight of the liver group was 125.7 in contrast to 133.8 in the pituitary group. If the final conditions of growth are to be inferred from the initial weight the lighter group or the younger would have the choice as here the growth would be most rapid. But this small difference of 8.1 grams would in no case explain the large difference in weight at the termination of the experiment.

These results are intensified by a further differentiation in which the initial and terminal weights are calculated separately for the rats which died and those which are still living. Upon comparing the thyroidectomized animals which died it was found that the liver-fed individuals lost weight, 111.0 grams to 104.2 grams, while the pituitary-fed rats gained, 88.7 grams to 125.4.

Thus an inspection of the experimental data shows that the administration of anterior lobe to thyroidectomized rats has a pronounced beneficial action improving their general condition, accelerating their growth and prolonging their lives.

The cause of death in the operated animals is not certain. That it was due either to a thyroid or a parathyroid deficiency is unquestionable since there was no evidence of infection and but one death of the controls. That the effect is produced by lack of thyroid is strongly indicated. The longevity of many of the animals after operation would exclude the parathyroid-deficiency hypothesis. It might be added that the duration of the experiment is longer than has been usually reported in studies upon thyroidectomized rats. Also, the general condition of the animals up to the time of death suggests a thyroid deficiency. Four of the animals which were not fed the anterior lobe exhibited typical myxedematous symptoms. By these I refer to the general appearance and habits of the animals. In most of the cases which died there was a marked dullness, the rats being somnolent and exhibiting a disinclination to move spontaneously. Since several individuals had been very wild and difficult to handle before the operation, the change to a dull, lethargic condition was very significant. The general nutrition was very poor, as the animals without exception in the liver-fed series were extremely emaciated just before death. The skin exhibited an appearance of lowered resistance, being devoid of hair in places and in four cases was covered with scabby sores. In the pituitary-fed animals which died, some showed emaciation but in no case was the condition so extreme.

#### DISCUSSION OF EXPERIMENTAL RESULTS

I have been unable to find any previous record of definite experimental data upon the results of the administration of the anterior lobe in cases of thyroidectomy, although there is good reason for considering this portion of the hypophysis.

Schäfer (51) states that the pituitary cannot take the place of the thyroid in operated animals, and that the pituitary extract is not able to take the place of the thyroid extract in the treatment of goiter and myxedema. However, he presents no evidence for this statement.

The clinical evidence upon substitution experiments is contradictory. Pineles (42) reported two cases of acromegaly with concomitant myxedematous symptoms. These symptoms were ameliorated by the administration of thyroid gland but were not influenced by pituitary tablets. This result was to be expected since the primary cause of the myxedematous symptoms was a hyperactivity of the hypophysis and therefore the addition of still more of the pituitary autacoid could have no effect. On the other hand, Pal (38) stated that infundibular extract was of value as a therapeutic agent in the treatment of hyperthyroidism. In his use of pituitrin the most noteworthy effect was that the patients felt so much improved subjectively that they requested the resumption of the treatment whenever it was discontinued. The effect was noticed only in those cases where the internal secretion was disturbed. Still more striking clinical evidence in favor of the functional relationship of the two glands is furnished by Richter (46); he reported that four cases of ambulatory Graves' disease were materially benefitted by the administration of desiccated anterior lobe over a considerable period. All of the cases exhibited well-marked characteristic symptoms of the disease and all, because of their circumstances, were forced to forego the advantages of complete rest and favorable hygienic treatment. However, remarkable improvement was secured and such symptoms as nervousness, the exophthalmos and tachycardia were ameliorated.

An analysis of the data furnished by the protocols of the present experiment indicates clearly that the administration of the anterior lobe of the hypophysis exerted a beneficial effect upon thyroidectomized rats. The action of the pituitary autacoid or autacoids not only ameliorated the condition of the operated rats, in which a deficiency of the thyroid hormone had been created, but actually lengthened the life of the animals. A favorable influence of the anterior lobe was seen also in the case of the normal rats where the coats and condition of nourishment were improved.

The question now arises as to the significance of these results. It has been assumed that in the absence or hypofunction of the thyroid there has been a direct functional substitution of the pituitary autacoid. Another possibility is that the beneficial action is not so much due to a functional relationship between the thyroid and hypophysis as to an

influence exerted by the pituitary substance upon the organism as a whole. In order to ascertain which of the above assumptions is correct, extensive, carefully controlled experimentation is necessary.

If the adherents of the Rogowitsch hypothesis are correct in their assumption that the hypertrophy of the hypophysis following thyroidectomy is physiological, then the favorable influence of pituitary feeding in cases of thyroid hypofunction is an indication of a direct substitution.

There are two objections to this idea of a functional reciprocity. The one is patho-histological in nature and the other is chemical. Trautmann advances the conclusion that the changes observed in the hypertrophied pituitary indicate a degeneration. Therefore the enlargement would indicate a pathological condition instead of a physiological hyperfunction. But these changes might well be the result of increased work or that the cells are taxed beyond their strength in the compensatory effort to perform a double function. Careful histological examination is necessary to ascertain whether there are any cellular evidences of increased functioning in the hypertrophied pituitary. In addition it is essential to discover the true significance of the increased production of colloid. If the colloid substance is to be regarded as an excretory product then its increased output would indicate increased activity upon the part of the cells. Most workers have reported an increased formation following thyroidectomy. The other objection sometimes advanced is based on the relative importance of the iodine content. The failure to detect iodine in the pituitary after thyroidectomy is considered as evidence contra-indicating a functional relationship, on the assumption that the iodine is an essential constituent of the thyroid autacoid. It certainly forms a large percentage of Kendall's thyroxin, constituting as much as 60 per cent. But Kendall emphasizes the indol group as the most important functionally and this same group might be present in the hypophysis or in Robertson's tethelin. On the other hand several investigators have expressed the opinion that the iodine is not an essential component. Again Kendall (31) states,

For reasons given hereinafter, it appeared desirable to emphasize the presence of the oxy-indol nucleus and it appeared equally desirable not to emphasize the presence of iodine.

He then proceeds to demonstrate that the physiological activity of thyroxin is due to the CO-NH groups.

In his explanation of some of the phenomena concomitant with thyroid disease and apparently anomalous exceptions, Kendall emphasizes

the necessity for the presence of some group similar in structure and function to that of the thyroid autacoid. Thus he states that patients with complete atrophy of the thyroid have a basal metabolism rate of 40 per cent below normal and that the administration of thyroxin alone can bring back and maintain the normal metabolism rate. Now he assumes the complete or nearly complete absence of thyroxin in complete atrophy. In answer to the question what maintains the energy output from 100 per cent below normal up to 40 per cent below normal (the point of basal metabolism in the absence of thyroxin), he assumes the presence of some chemical substance in the body with the *same groupings* as in thyroxin. According to his interpretation of the function of iodine, the halogen merely renders the active groups more reactive. Thus,

in the absence of iodine it would take a greater working pressure to bring about its reaction. The substitution of iodine by hydrogen or chlorine or bromine would undoubtedly be followed by an alteration in the degree of reactivity of the substance, but its *gross chemical nature and properties* would not be altered thereby. That the iodine breaks off from the molecule and is used as iodine per se for any purpose, seems absolutely impossible, because Plummer (44), has shown that this substance functions for as long as from 15 to 21 days after being administered . . . .

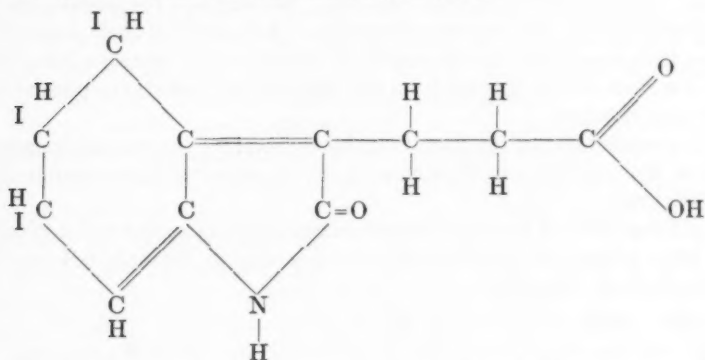
If the iodine plays a minor rôle, how are the beneficial effects of iodine therapy to be explained? Kendall allocates the symptoms of hyperthyrosis following the administration of iodine to the excessive liberation of thyroxin caused by the stimulating action of iodine, since thyroxin in large amounts will produce hyperthyroid symptoms. Again, the beneficial effects of iodine in myxedema depend entirely upon the amount of active thyroid substance. If the ill effects are due to a partial failure of the gland to maintain a normal supply of thyroxin, the administration of iodine would enable the thyroid substance to make sufficient thyroxin. On the other hand in the condition of complete atrophy no amount of iodine would avail. Again, he considers the animals with the iodine-free thyroids to be analogous to myxedematous individuals in which there is a complete atrophy of the thyroid and a metabolic rate below normal. Here again some other group must be present.

Shumway (55) clearly differentiates between the action of iodine and the thyroid active principle in his experiments with paramecia. He reported that thyroid substance produced an increase of growth of sixty-five per cent in the rate of division while iodothylin and iodine failed to give this effect.

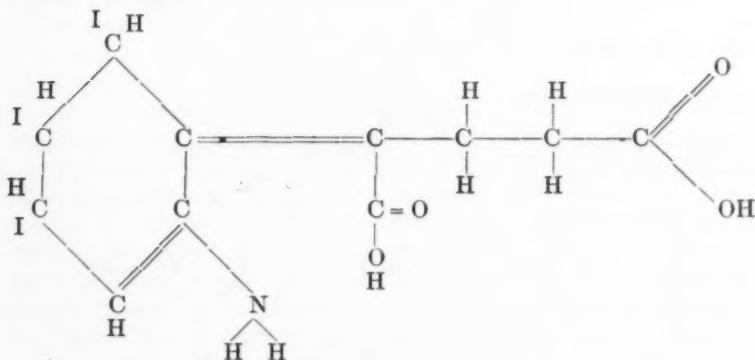


If the above reasoning is correct the objection advanced by Simpson and Hunter, based on the failure to detect iodine in the hypophysis of thyroidectomized animals, has slight significance, if any. Even if iodine were assumed to be vital to the thyroid substance there could still be a substance so nearly similar in structure and function in the hypophysis that upon a diminution of the former, the latter could be substituted with partial or complete success.

In this connection it is of interest to note the possible similarity in structure between the active principles of the two glands. According to Kendall, thyroxin has the following structure:



He further stated that within the body the indol ring opens up assuming the structure:

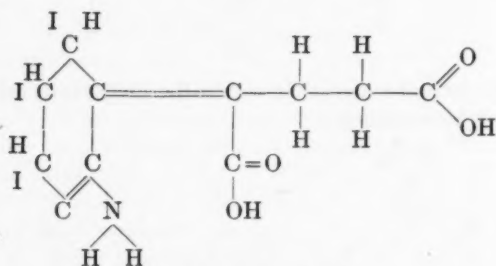
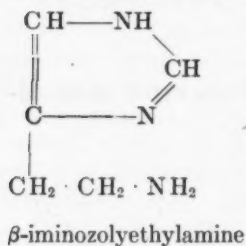


On the other hand two different substances have been isolated from the hypophysis. The researches of several investigators have empha-

sized the similarity between the properties of the active principle of the posterior lobe and  $\beta$ -iminozolyethylamine. Some have gone still further and identified the two substances. For an excellent discussion of the active principle of the posterior lobe Barger's *The Simpler Natural Bases* (4), and the work of Schmidt and May (52), should be consulted. The only supposedly active principle which has yet been isolated from the anterior lobe is tethelin, considered by Robertson (47) as the active principle, par excellence. Since Robertson found  $\beta$ -iminozolyethylamine in tethelin the idea was advanced that the tethelin was the mother substance of the  $\beta$ -iminozolyethylamine of the posterior lobe. Accordingly, Schmidt and May (52) studied the physiological activities of the split product of tethelin. As a result of their investigation they concluded that the active substance of the posterior lobe was to a certain extent derived from the splitting of a substance present in the anterior lobe.

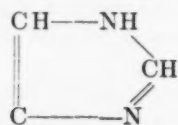
A consideration of the literature shows therefore an unanimous agreement that  $\beta$ -iminozolyethylamine as a very important principle in the hypophysis.

A comparison of the structures of  $\beta$ -iminozolyethylamine and thyroxine at once reveals the presence of a benzene ring in thyroxine but not in the pituitary principle.

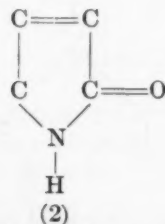


However, there is a closed ring in each.

Thyroxine, open form.



and



(1)

(2)

Closed ring of  $\beta$ -iminozolyethylamine.

Closed ring of thyroxine.

If the closed form of thyroxin opens in the body it would not be unreasonable to assume that the grouping (1) could also open up at its most reactive point, the  $\text{NH}_2$  radical, and function in place of the thyroid ring.

The structural analysis of the known autacoids of the two glands, therefore, reveals a sufficient similarity to indicate the possibility of substitution. In addition to this similarity in chemical structure, a study of the two glands in relation to metabolism brings forth further correlations. A removal of either gland causes disturbances in carbohydrate and fat metabolism, as well as in the sexual activities and general growth of the body. Therefore even if no iodine be present after thyroidectomy, in view of the similarities noted, it is reasonable to assume that the pituitary hormone can, in a time of thyroid deficiency, take the place of the latter in the metabolic processes.

Still further evidence in favor of the idea that the hypertrophy of the pituitary is physiological is furnished by the experiments of Livingston (35), who reported that thyroid feeding in thyroidectomized rats did prevent the hypertrophy. It would be interesting to note whether pituitary feeding would also prevent the hypertrophy.

Again, Hoskins interprets the hypertrophy of the pituitary in thyroidectomized amphibian larvae as being physiological. His assumption is based upon the subsequent gigantism noted in thyroidless larvae.

To recapitulate, the objections to the idea of a direct vicarious relationship are twofold: the failure to find iodine in the hypophysis after thyroidectomy and the possibility that the hypertrophy indicates pathological processes. On the other hand there is the possibility that the hypertrophy is physiological and that the iodine might not be a necessary factor. There are also similarities in chemical structure and functions.

Before a definite decision for or against the idea of a direct functional reciprocity can be reached, more evidence is needed. That such a reciprocal relation might be one-sided, is indicated by clinical substitution experiments. Although it may be assumed that the pituitary does, in time of a thyroid deficiency, function for the latter, the thyroid apparently cannot take the place of the hypophysis. Thus Climenko (11) reported a case of infantile hypopituitarism in which there was an absence of distinct myxedematous symptoms and no response to thyroid medication but a decided amelioration after the administration of pituitary extract, the whole dried gland. Again, Stephenson (58) applied thyroid therapy to a case of dyspituitarism without success.

Instead of a functional reciprocity it might be supposed that the beneficial effects obtained are due to an excess of pituitary hormone which affects the organism as a whole. That this would very well be the actual rôle of the hypophyseal substance is possible when the widespread disturbances are noted which result from pathological conditions. Thus to quote Falta (20), page 250:

The regressive changes in the thyroid gland that so frequently become established in the later stages of acromegaly might well be regarded as a partial phenomenon of the degenerative alterations that in the later stages of acromegaly involve not only these organs that are the seat of the tendency to grow fostered by acromegaly, but also the entire body as well. Hence in the later stages of acromegaly we may often see myxoedematous symptoms, even in the absence of previous manifestations of hyperthrosis.

Again:

The vascular system in the later stages of acromegaly almost always shows changes . . . . not rarely in addition to the enlargement of the heart there is found an enlargement of the liver, the spleen, the stomach and the intestines . . . . kidneys . . . . suprarenals . . . . In many cases the pancreas was found to be sclerosed . . . . and often of enormous size. A persistent thymus . . . . has been reported quite frequently . . . . The examination of the blood in acromegaly shows not rarely a reduction in the number of erythrocytes and in the hemoglobin contents. . . . In the majority of cases the differential count shows a mononucleosis and not rarely an increase in the number of eosinophiles.

Important abnormalities of metabolism are also associated with the disease. Some of the more important are disturbances in fat carbohydrate and salt metabolism; spells of polyphagia. Attention has been called repeatedly to changes in function of the genital glands, and condition of the vegetative nerves and often a wasting away of the body.

An enumeration of the above symptoms concomitant with hyperpituitarism or acromegaly is indicative of some of the ways in which the hypophysis might affect the entire organism. These conditions are supposedly due to an excess of the hypophyseal substance which resulted from an abnormal condition of the anterior lobe. Since there is such a remarkable correlation between the hypophysis and the other organs, it is but natural to infer that in case of a physiological or pathological dearth of the thyroid hormone the pituitary might tend to restore the normal equilibrium. Evidence that this does actually occur is found in a compensatory hypertrophy. On the other hand, an excess of hypophyseal substance administered would now cause not pathological alterations in the other organs but a restoration of the normal "hormone balance."

## SUMMARY

1. The administration of the anterior lobe of the hypophysis has a very beneficial action upon the maintenance and growth of thyroidectomized rats. Aside from the ameliorating effect upon the general condition of the animal, the life is definitely prolonged.

2. The beneficial effect might indicate a direct substitution in which the pituitary autacoid takes the place of the thyroid hormone in a compensatory effort to establish normal metabolism. Or the results obtained might be due to a stimulating effect upon the total metabolic processes. A definite decision can only be obtained by extensive study of the various factors involved.

3. An attempt has been made to summarize the existing evidence for a possible direct substitution and to answer objections to this explanation of the results.

The writer wishes to express his appreciation of Prof. S. S. Maxwell's counsel and interest throughout the entire investigation. He is also indebted to Miss L. Burke for her personal assistance in carrying out the experiment.

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## STUDIES IN SECONDARY TRAUMATIC SHOCK

### I. THE CIRCULATION IN SHOCK AFTER ABDOMINAL INJURIES

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When the Physiological Committee of the National Research Council adopted as part of its war program a coöperative investigation of surgical shock, this laboratory decided to devote itself to the study of those phases of the problem to which its facilities seemed best adapted. Formal, though brief reports on the progress of the work have been made to the Committee from time to time, and a few brief preliminary notes covering certain phases of the problems have been published (1), (2), (3). Now, with the cessation of the urgent press of war work, time is taken to prepare more complete reports of our experiments.

It is well at the outset to set forth clearly the condition it was our intention to study. In this connection the distinction must be drawn sharply between so-called primary and secondary shock, a distinction more readily drawn in the case of man than of animals. According to Cowell (4) in *primary shock*

the man suddenly becomes pale, clammy, and pulseless; and a low pressure may be found as soon as it is possible to make a reading, 15 to 20 minutes after the man has been hit.

When, on the other hand . . . a (wounded) man previously in good condition develops similar shock symptoms, a condition of *secondary wound shock* may be said to exist.

Whether or not there are grounds for believing that these are two wholly different conditions is a question that does not concern us here. But it is important to bear in mind that the conditions studied in the laboratory presumably resemble secondary more nearly than primary shock as defined by Cowell.

One of the problems with which all were at first concerned was how to recognize and how to produce "shock" in animals. In his first communication on the subject, the Chairman of the Physiology Committee

suggested that the criteria of shock enunciated by Mann (5) be taken as our standard. These are: *a*, "loss of sensibility, as shown by the lack of the necessity of administering an anesthetic when the eye reflex is present;" *b*, "pallor of the mucous membranes;" *c*, "a small, weak pulse;" *d*, an "irregular, rapid, shallow or gasping respiration;" and *e*, a blood pressure lowered to one-third or one-fourth its original level. These signs are not all equally easy to recognize. For this reason, and for others also, we were not always certain that we had succeeded in getting into this condition all the animals which we had good reason for believing were in "shock." In the dog, the eye reflex is a most uncertain index. An animal certainly not in "shock" may have no reflex whatever; and on the other hand, it may, of course, be absent in animals in "shock." Again, animals in "shock" with eye reflex either present or absent, may begin to move shortly after the anesthetic is removed; though to be sure, in every case of "shock," properly so-called, only the lightest anesthesia is necessary to keep the animal quiet. Furthermore, Mann's blood pressure criterion is usually an altogether impossible one. The arterial pressure at the beginning of our experiments most often lay between 100 and 125 mm. Hg., sometimes lower, sometimes higher. Taking Mann's larger fraction, namely, one-third, these animals, according to his criterion would not be in "shock" unless their pressures had fallen to 33 to 40 mm. Hg.; or, taking his smaller fraction, one-quarter, to 24 to 31 mm. Hg. But when, during the induction of shock, the pressure passes below 40 mm. Hg., the animal has passed beyond shock—it is dying. As a matter of fact, Mann himself does not adhere to this specification (6).

We do not believe that in the present state of our knowledge shock can be defined to the entire satisfaction of all. And yet, for any given investigation of the subject it is necessary, in order to be able to compare the results of different procedures, to have some standard state to compare. A fall in arterial pressure is certainly one of the manifestations of developed shock and there can be very little reason for doubting that the state of shock is present when, as a result of traumatization, the blood pressure has fallen slowly but consistently to the level of 50 mm. Hg. Indeed it is almost safe to state when the arterial pressure has thus fallen to this level that the circulatory failure has become irreversible; though to be sure by certain procedures, such as the administration of adrenalin, the arterial pressure can be raised temporarily. Clinical experience is in accord with this opinion. Thus, according to Archibald and McLean (7), cases in which the systolic and diastolic

pressures fall as low as 75 and 40 mm. Hg. respectively, rarely recover. The geometric mean of this pulsatile range of pressure cannot be very far from 50 mm. Hg. There are other reasons for selecting 50 mm. Hg. as the level for comparison. If an animal with a pressure of 50 mm. Hg. is not in shock it is only a question of time, if this pressure is maintained, before shock properly so-called will supervene. In other words any procedure that will carry the arterial pressure down to about 50 mm. Hg. and hold it there for a sufficient length of time will, if it does not lead too rapidly to dissolution, bring on the picture of shock. Furthermore, it frequently happens, when an animal is exposed to conditions that lead a shock-like failure of the circulation, that after the arterial pressure begins to fall the descent is relatively rapid until the pressure comes to lie somewhere between 60 and 40 mm. Hg., when it is apt to become less rapid, so that the pressure for hours may hover in the vicinity of 50 mm. Hg. before the more rapid fall begins that leads to death. We realize, as one of us has emphasized (8), that the circulation may be severely disturbed, as indicated by a reduced volume flow of blood, even before the blood pressure begins to fall. But unfortunately there is at present no satisfactory or convenient way of recognizing in man the imminence of shock through the use of this particular sign. For these reasons we adopt in this investigation a blood pressure criterion of shock and arbitrarily take the level of 50 mm. Hg., when certain other signs also are present, as surely indicative of the presence of shock.

The procedures we have employed for the purpose of bringing on shock can best be described in connection with the several sets of experiments we have performed. Their significance in relation to the mechanism of shock will be considered in the final discussion.

#### GENERAL METHODS

For the most part the animal employed in this investigation has been the dog. All were anesthetized with ether. At first a preliminary dose of morphine was administered but, gaining the impression—by no means, though, a conviction—that the morphine delayed the onset of shock, the use of morphine was soon discontinued. Throughout the experiment the anesthesia was as light as possible and usually quite uniform.

*Arterial and venous pressures.* The carotid pressure was followed by a mercury manometer throughout all of the experiments. In some

experiments the portal pressure also was followed either continuously or from time to time. In these cases the jugular pressure also was recorded from time to time. The former pressure was taken from the vena gastro-lienalis. This vein is easily exposed through an abdominal incision just large enough to permit of the delivery of the spleen, and without exposing or even touching the intestines.

The main difficulties to be overcome in recording the venous pressures through prolonged experiments, besides obviating the action of valves, consist in the recognition and the prevention of obstruction by coagulation, by kinking or by extraneous objects. These difficulties we have succeeded in minimizing through the use of the following method: An obliquely bored three-way stopcock is so connected with a pressure bottle containing salt solution, in which is dissolved 0.01 mgm. hirudin per cubic centimeter, with a manometer, and with the vein that by turning it into one position the manometer can be raised until it records a pressure slightly in excess of the anticipated venous pressure, whereupon, by turning the cock into the other position, the manometer is thrown into communication with the vein and sinks to the level of the venous pressure, a corresponding volume of hirudin solution, usually not more than 0.05 cc., running into the vein. This manipulation is repeated at intervals of about five minutes throughout the course of the experiment. The total volume of hirudin solution thus washed into the circulation need not exceed 10 cc. even in the longest experiment. Clotting has rarely occurred. The method quickly discloses any interference with the transmission of the pressure back from the portal vein, when the readings are taken from the splenic vein, or back from the right auricle, when the readings are taken from the jugular vein. The importance of such a means of control when the record, as is often the case, may be without any oscillation whose diminution or cessation would disclose an obstruction, cannot be over-emphasized. Methods resembling ours have been employed by other investigators.

*Inflow method.* The tone of the peripheral arteries has been followed by means of a modification of a method previously employed in this laboratory by Bartlett, also in a study of shock (9). From time to time determinations are made of the rate of flow of salt solution under a constant pressure, one so high as to nullify the effects of changing venous and collateral (arterial) pressures, through a part of the peripheral resistance from time to time momentarily isolated in such a way as not to injure the nerves or the nutrition of the part concerned. The method differed from Bartlett's only in that the injection period was

both controlled and recorded electro-magnetically; it was thus freed entirely of the errors inherent in reaction time.

For the most part, the injections ("inflows") were into the hind-leg ("femoral") area; though a few have been made into an intestinal area and into the liver. When the intestine was employed care was taken not to handle or even to remove from the peritoneum the part into which the injection was to be made. Examination at the close of the

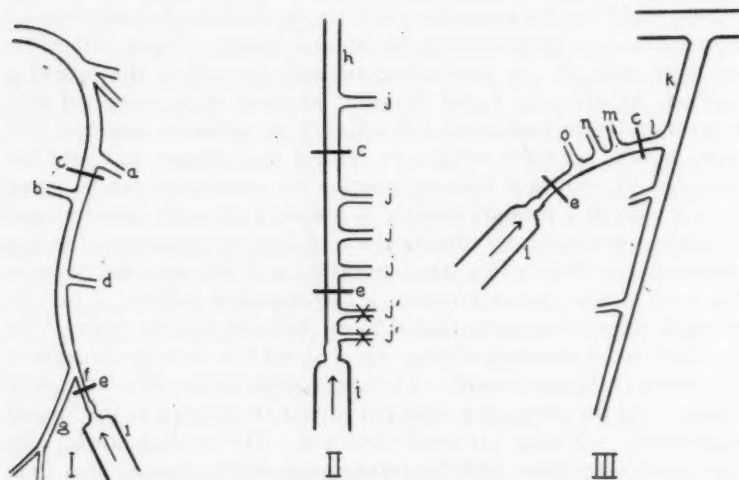


Fig. 1. Diagrams showing the arrangements for inflow experiments.

I. Femoral inflow. Main branches of the Arteria femoralis with the position of the inflow cannula, *i*, of the electromagnetic obturator, *e*, and of the clip *c*. *a*, A. profunda femoris; *b*, A. femoralis anterior; *d*, A. femoralis postica superior; *f*, A. saphena; *g*, A. articularis genu suprema.

II. Intestinal inflow. *j*, Aa. ileae (*j'*, ligated) of *h*, A. mesenteria superior.

III. Hepatic inflow. Main branches, *m*, Ramus hepaticus dexter; *n*, Ramus hepaticus sinister; and *o*, Ramus hepaticus medius of *l*, A. hepatica; *k*, A. coeliaca.

experiment showed that the perfused area usually included one or two loops of the lowermost part of the ileum.

The diagrams shown in figure 1 will serve to indicate how and where the injections were made. To determine the inflow rate, the clamp, *c*, is first adjusted on the artery. Then, by operating the electromagnetic obturator, *e*, with a chronographic marking key, salt solution under a high pressure is permitted to run into the artery, in the direction shown



by the arrow, for from three to five seconds, rarely longer; then the clamp, *c*, is removed. Under ordinary circumstances, the circulation of the part receiving the solution is stopped not over a half-minute for each estimation. The inflow period employed has been such as would allow about 2 to 6 cc. of solution to enter the circulation, the considerations being to allow in a sufficient volume to minimize the effect of distention of the arteries and of the changing viscosity, and yet not inject into the circulation a volume of salt solution so large as to materially affect the general trend of the state of the circulation. The total volume injected before the arterial pressure reached the level of 50 mm. Hg. exceeded 100 cc. in only three experiments, and usually it was considerably less; and the total injected before death, excepting cases in which injections were made for special purposes, in only two instances exceeded 200 cc. As the injection of this total quantity usually extended over a period of many hours, it may be regarded as relatively small in amount. If it had any other than the usual transitory effects on the circulation, we were unable to recognize them. A continuous perfusion method, such as that of Sollmann and Pilcher (10), would have been preferable; but in experiments lasting as long as have these, such a method is precluded by the tremendous edema that eventually develops. The method of Morison and Hooker (11) seemed objectionable on account of the possible consequences of the great change in vascular bed that is made in association with the period of observation.

Bartlett tested the inflow method and found that it revealed changes in peripheral resistance, and that other physiological changes in the circulation were without influence on it. We have completely confirmed Bartlett's tests. The accuracy of the method cannot be measured in absolute terms; but the experiment illustrated by figure 2 demonstrates, by the regularity of the form of the curve as the vasomotor tone dies away after the extreme constriction produced by cerebral anemia, that variations in peripheral resistance are correctly indicated.

Precautions must, of course, be taken to avoid adventitious plugging of the blood vessels. Our results show that if any plugging did occur, in at least the vast majority of cases it was not sufficiently extensive to mask the main effect. In very long experiments clots sometimes form in the main artery just in front of the cannula. To insure against vitiation of results by an unrecognized partial obstruction of this kind, the rate of inflow into the unclipped artery during a fraction of a second was noted from time to time, and inflow readings were accepted only when the rate of flow into the unclipped artery greatly exceeded the rate

of the flow into the clipped artery. If a clot did form and could not be forced on into the general circulation (not into the part perfused), determinations were continued on the femoral artery of the other side; or if the artery perfused happened to be unpaired, inflow readings were discontinued. When the transfer is made from one femoral to the other, the new *normal* inflow rate is unknown. This, however, is of but little consequence; for the method is relative only, and if the conditions

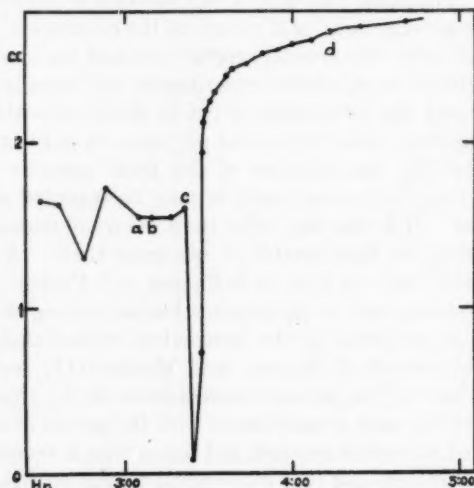


Fig. 2. Illustrating the capabilities of the inflow method (femoral). A reading was made at *a* simultaneously with a peripheral stimulus of the vagus that stopped the heart; it shows that a mere fall in arterial pressure, before time for reflex effects has elapsed, is without effect on the inflow rate. At *c* the ventricles were fibrillated; the subsequent readings show the effect of extreme asphyxial stimulation of the centers, followed by its death. At *d* the great veins were cut; the result (no change) shows that venous back pressure is without effect on inflow rate.

at the time of the transfer are fairly constant, the first of the new series of inflows may be taken as a new level from which to regard the trend that obtained while the last of the old series were made. And, in any event, the normal inflow times of the two femorals of any one animal are probably very nearly alike.

In each experiment the animal is first made entirely ready for the induction of shock; that is to say, all of the preliminary operations and

cannulations are made. Then from one to eight, usually three, inflow readings are made for the purpose of determining the normal vasomotor tone. These readings, however, are rarely if ever constant; indeed they usually fluctuate widely, as widely as the vasomotor tone is known to fluctuate normally. It was easy to demonstrate that at least some of these early fluctuations were vasomotor reflexes started by some definite manipulation, such, for example, as placing the clip upon the artery. It is interesting to note that as a rule the readings become much more regular as the experiment proceeds; for this observation indicates that the vasomotor reactions diminish with time. Although the wide fluctuations in inflow rate at the opening of the experiment made it difficult to determine the norm, yet they served the useful purpose of proving that in the preparations for the experiment the nerve supply to the peripheral resistance concerned had not been injured. It is possible that by the time the preliminary inflow readings are obtained a certain amount of peripheral constriction already has developed (8).

*Charts of results.* In order to simplify the analysis of the lengthy records the results have been plotted on a system of coordinates. We are reproducing a number of the curves thus constructed so that those who are working on shock may have the opportunity of seeing the data upon which our conclusions are based. In reading these charts it should be borne in mind that the venous and arterial pressures are plotted on different scales; to bring out sharply the small fluctuations in venous pressure, large ordinates are necessary. It should also be borne in mind that vasomotor tone is the reciprocal of the "inflow rate."

#### THE CIRCULATION IN SHOCK AFTER ABDOMINAL INJURIES

In this paper the results are given of our study, by the methods described above, of the mechanical changes in the circulation occurring during the development of shock by procedures directly affecting the abdominal viscera.

#### SHOCK BY EXPOSURE AND MANIPULATION OF THE INTESTINES

Ten experiments of this character have been performed. In table 1 it is seen (exps. 7, 8, 9, 10, 19, 21, 26, 58 and 59) that, disregarding the preliminary procedures, the experiments lasted from  $5\frac{1}{2}$  to 11 hours each, and that the pressure level of 50 mm. Hg. was reached in from  $3\frac{1}{2}$

to about  $7\frac{1}{2}$  hours, most often in about 5 hours. In one case it had not fallen to that level even after 11 hours had elapsed. When calculated, however, from the time manipulation of the intestines was begun, and

TABLE 1  
*Shock after abdominal operations*

EXPERIMENT NUMBER	DURATION OF EXPOSURE *	PRESSURE ABOVE 50 MM. HG.	PRESSURE 50 MM. HG. OR BELOW	MANIPULATION BEGUN AFTER EXPOSURE	BETWEEN MANIPULATION AND 50 MM. HG.	REMARKS
	hours	hours	hours	hours	hours	
7	6	$3\frac{1}{2}$ - $4\frac{1}{2}$	$1\frac{1}{2}$ - $2\frac{1}{2}$	3(?)	$\frac{1}{2}$ - $1\frac{1}{2}$	Exposure and manipulation
8	8	$6\frac{1}{2}$	$1\frac{1}{2}$	$2\frac{1}{2}$	4	Exposure and manipulation
9	$5\frac{1}{2}$	5	$\frac{1}{2}$	$\frac{1}{2}$ (?)	$4\frac{1}{2}$	Exposure and manipulation
10	$6\frac{1}{2}$	$3\frac{1}{2}$	3	$\frac{1}{2}$	3	Exposure and manipulation
19	8	6	$1\frac{1}{2}$	$1\frac{1}{2}$	4	Exposure and manipulation. Long preliminary operation involving manipulation of intestines
21	$7\frac{1}{2}$	$5\frac{1}{2}$	$2\frac{1}{2}$	3+	2	Exposure and manipulation. Long preliminary operation involving manipulation of intestines
26	11			$\frac{1}{2}$		Exposure. Scarcely shocked after 11 hours
58	6	$5\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	5+	Exposure and manipulation. Position of inflow cannula prevents thorough manipulation
59	$9\frac{1}{2}$	$7\frac{1}{2}$	2	$\frac{1}{2}$	7	Exposure and manipulation. Position of inflow cannula prevents thorough manipulation
13	$6\frac{1}{2}$	3	$3\frac{1}{2}$	**	**	Evisceration
16	6	5	1	**	**	Evisceration
17	5	$2\frac{1}{2}$	$2\frac{1}{2}$	**	**	Evisceration
22	2+	0	2			Exposure in sympathetic-less animal
23	6	3-	$3\frac{1}{2}$	$\frac{2}{3}$	$2\frac{1}{2}$	Exposure and manipulation in sympathetic-less animal

\* The time necessary to make the preliminary operation is not included.

\*\* Evisceration was performed immediately and required about 15 minutes.

when this was thorough, this fall was accomplished most often in about 4 hours. It is also seen that the pressure was 50 mm. Hg. or lower for from 20 minutes to 3 hours, most often for about  $1\frac{1}{2}$  hours.

*Peripheral resistance*

*Femoral inflow.* The early effect on the femoral inflow rate of exposing and manipulating the intestines has not been entirely constant; it is fair to say, though, that practically invariably the inflow rate is reduced, and usually below the initial range (see figs. 3, 4, 5, 8, 9). This constriction as a rule persists through the period of maintained arterial pressure and often for some time after the arterial pressure begins to fall (figs. 3, 4). It then gradually gives way to dilatation, so that by the time the arterial pressure has fallen to the level of 50 mm. Hg., the

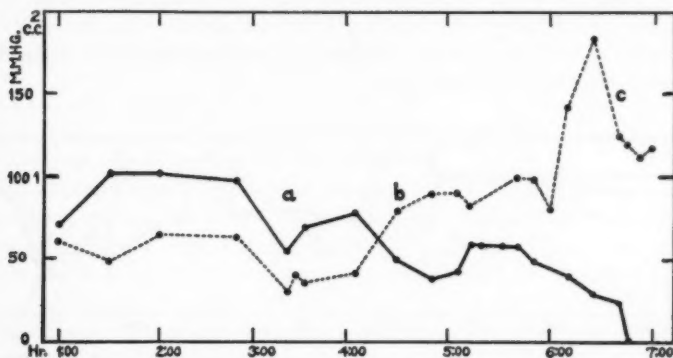


Fig. 3. Experiment 7. Shock by exposure and manipulation of the intestines. Arterial pressure, —•—•—; femoral inflow rate, - - -•- - - . a, some time after exposure and manipulation; b, three minutes after manipulation; c, asphyxiated to end.

inflow rate practically without exception has been as high as, or higher than, the highest initial inflow rate. As the end approaches, the inflow rate often accelerates (figs. 3, 8). Sometimes there is a retardation (asphyxial) at the moment the heart or respiration stops, followed by an acceleration (figs. 5, 8, 9). In some cases a mortal increase in the inflow rate has failed to occur; indeed the asphyxial decrease occurring at this time sometimes has failed to pass off entirely (figs. 3, 4, 9).

This occasional failure of the inflow rate to increase beyond the normal after death is worthy of a moment's consideration. It has been seen not alone after exposure of the intestines but as a matter of fact at the conclusion of long lasting experiments in general and also after adrenalin injections in experiments of even short duration. In part,

at least, it is due to constriction of the larger arteries, including the femoral itself; for the rate of flow through the unclipped artery at this time may be but little faster than the rate through the clipped artery. The first explanation of this phenomenon that suggests itself is that it is due to the formation of an obstruction (a clot) in the artery. But this conclusion is rendered untenable by the behavior of subsequent inflows; for these almost invariably slowly increase from trial to trial (see, for example, fig. 4). The only explanation of the phenomenon that seems at all to fit the facts is that as a result of prolonged asphyxia the arteries pass into a state resembling post-mortem contraction, such as has been described by MacWilliam (12). It is worthy of note that Sollmann and Pilcher (13) found that in post-mortem paralysis of the vasomotor center the outflow, followed by their method, also often did not quite recover its former rate.

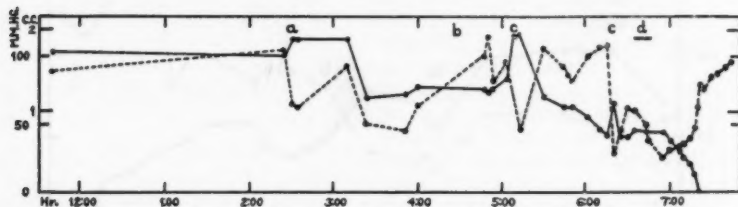


Fig. 4. Experiment 8. Shock by exposure and manipulation of the intestines. Arterial pressure, —•—•—; femoral inflow, ---•---. a, intestines exposed; b, changed from left to right femoral artery; c, adrenalin, 1.0 cc. 1:20,000, intravenously; d, asphyxia.

*Mesenteric and hepatic inflows.* No lengthy explanation is needed to make it clear that mesenteric and hepatic inflows can be followed only with great difficulty in experiments in which the intestines must be exposed and manipulated in such a way as to protect and leave undisturbed the part into which the injection is being made. We have succeeded in making fairly satisfactory observations in three of the experiments. The results, upon the whole, have been the same as in the case of the femoral inflow.

In one of the experiments (fig. 5) both the femoral and hepatic (actually hepato-duodenal) inflows were followed. If allowance is made for the fact that the hepatic and femoral readings were not made simultaneously, the general parallelism of the two inflow curves, excepting the readings made after death, is striking. Some time after manipulation



of the intestine, and at a time when the arterial pressure reaches about 50 mm. Hg. (5:30), both of the inflow readings are high, the hepato-duodenal being well above the initial range, the femoral at about the upper limit of normal. The terminal (presumably asphyxial) slowing of the femoral inflow rate is followed by the usual post-mortem acceleration; that of the hepatic, however, is not, possibly because a clot was beginning to form.

In experiment 21 (fig. 6) the hepatic and intestinal inflows were followed. The former showed no consistent changes. It should be noted, however, that at *b* (see fig. 6) it became necessary to force a clot on into the hepatic circulation. The intestinal inflow was not redetermined until the arterial pressure had fallen to 50 mm. Hg. some 3 hours after exposure of the intestines. The inflow rate then was well above normal. Then, after a lapse of 40 minutes, the inflow rate was found to be markedly diminished and it remained so to the close of the experiment. This final decline of the inflow rate might have been due to the slow formation of an obstruction (clot).

In experiment 26 (fig. 7) the intestines were merely exposed (at *a*) and not manipulated. After 10 hours of exposure, the arterial pressure was still 80 mm. Hg., but finally it fell to 52 mm. Hg. After it had been at the latter level for 4 minutes a clot formed in the inflow artery. The experiment was then brought to a close by puncturing the heart. Exposure of the intestines in this experiment led to a very marked reduction in the intestinal inflow rate over a period of 8 hours. Then the inflow rate increased. It reached practically the low limit of normal and was still on the increase at the time the last reading was made.

Although these experiments cannot be regarded as entirely satisfactory, they nevertheless clearly confirm the results obtained in the study of the femoral inflow rate and indicate that in shock produced by exposure and manipulation of the intestines the hepatic and intestinal (splanchnic) areas, as well as the femoral (somatic) area constrict, or, at least, do not dilate, during the early stages of shock induction and dilate as the pressure falls toward the level of 50 mm. Hg. The differences in the behavior of the intestinal inflows in the different experiments possibly are attributable to differences in the amount of handling the intestines suffered, and also to the time relation obtaining between the actual handling of the intestines and determination of the inflow rate.

The behavior of the arterial pressure and of the inflow rate as we have described and pictured them applies to the conditions obtaining while the intestines are lying quietly out of the abdomen in the intervals

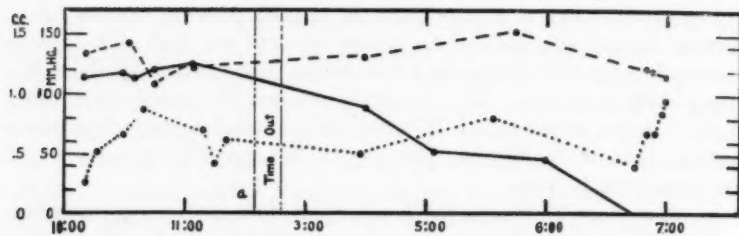


Fig. 5. Experiment 19. Shock by exposure and manipulation of the intestines. Arterial pressure, —•—•—; femoral inflow, .....; hepato-duodenal inflow, —•—•—, a, manipulation of intestines.

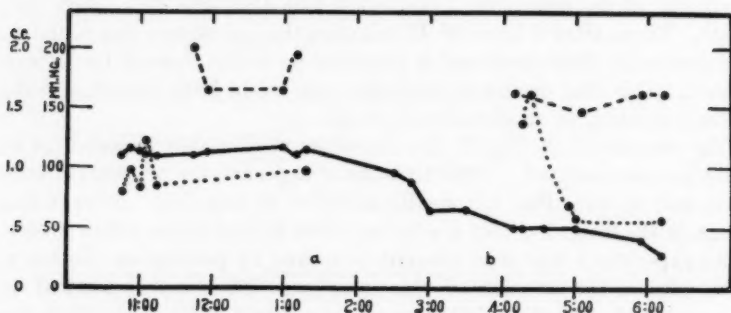


Fig. 6. Experiment 21. Exposure and manipulation of the intestines. Arterial pressure, —•—•—; intestinal inflow, .....; hepatic inflow, —•—•—, a, intestines exposed; b, clot in hepatic cannula forced on into capillaries (hepatic).

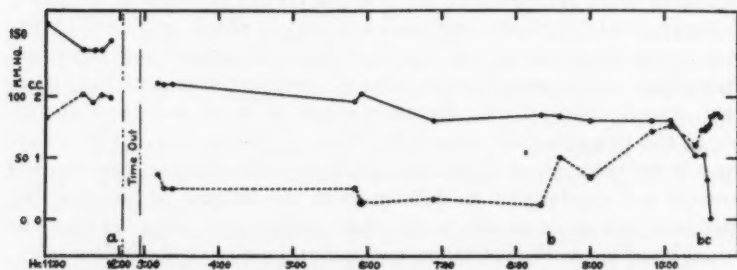


Fig. 7. Experiment 26. Exposure of the intestines. Arterial pressure, —•—•—; intestinal inflow, .....; hepatic inflow, —•—•—, a, intestines exposed; b, clot removed from inflow cannula; c, animal killed by puncturing heart.

between manipulations. When observations are made during, or very shortly after, momentary, though it may be, rough, manipulation of the intestines the result, at least during the first hour or two of the period of shock induction, is quite different. The immediate effect of manipulation then (see fig. 3, *b*) is a sharp fall in arterial pressure and a momentary, and it may be marked, increase in (femoral) inflow rate. This unquestionably is a passing reflex dilatation. The relation this reflex bears to the basic change in peripheral resistance occurring during shock development has not been investigated.

*Interpretation and discussion.* Interpretating our results in terms of activity of the vasomotor center, it can be stated categorically that in the early stages of exposure of the intestines the tone of the center usually is increased; that by the time the arterial pressure has fallen to 50 mm. Hg. the tone of the center practically invariably is subnormal, but never is entirely lost. The latter finding confirms Bartlett (9). But even when the tone of the center is subnormal it still is capable of responding in the usual manner to asphyxia produced by suffocation or by sudden stoppage of the heart. The constrictions so induced, though, are very much smaller than those occurring in normal animals. In the last stages of the experiment, therefore, the condition of the center is below normal as regards both its tone and its reactivity.

The fact that vasoconstriction is the rule while the pressure is still high and that dilatation occurs as a rule only after the pressure has been low for some time, would seem to indicate that exposure of the intestines in some way tends to cause a fall in pressure, but that this tendency is combated by the vasoconstrictor center; and that this hyperactivity is maintained as long as the arterial pressure is high enough to maintain a sufficient supply of blood to the centers. It sometimes happens, however, that the inflow rates are not diminished even when the arterial pressure has begun to fall (fig. 8). In such instances, which have been very rare, it must be concluded that the reactivity of the center to lowered pressure is subnormal.

As is well known, there is a large literature, full of contradictions, on the state of the vasomotor center in shock. Inasmuch as practically all these views rest upon observations on, or inferences drawn from, shock as produced by exposure of the intestines or by some comparable procedure, a brief discussion of this subject is here in order.

One cause of the misunderstandings that have arisen in the discussion of this question seems to be a tendency on the part of those holding definite views to overstate the antagonistic views. Thus, those who

have maintained that the cause of shock is to be sought in fatigue, or depression, or exhaustion, or inhibition of the vasomotor center did not as a rule intend to imply, as some seem to believe, that the center is wholly without tone, or wholly unresponsive to its normal stimuli. While another cause of the discrepancies probably is revealed by the fact, brought to light by the present investigation, that the state of vasomotor tone is not the same in all stages of shock. Doubtless different investigators have been dealing with different stages of shock. An analysis of some of the more important contributions to this subject, with these sources of error in mind, will serve to make our contention clear.

It should be stated in the first place that the origin of the view that shock is due to diminished vasomotor activity rests upon inferences from clinical data and from indirect experimental data rather than upon direct methods of attack (14), (15), (16), (17), (18). Porter and collaborators (19), (20), (21), were the first to approach the problem with a view to testing the then prevailing hypothesis by more direct means than had previously been employed. They succeeded in showing that the fall in arterial pressure on stimulation of the depressor nerve, and that the rise in arterial pressure on stimulation of other afferent nerves are proportionally as great in shocked as in normal animals. They, therefore, maintain that the activity of the vasomotor center is not impaired in shock. Lyon and Seelig (22) using a similar method independently come to the same conclusion. Sollmann and Pilcher (23) rightly take exception to this method because of a fallacy in the underlying logic. They point out that a percentile rise in pressure, other things being equal, denotes some loss in activity on the part of the center; that an unimpaired center should be capable of producing an unimpaired absolute rise in blood pressure. Indeed, it is to us conceivable that a percentile rise might actually occur where the center is overactive. Thus a normal center that is stimulated to hyperactivity by a reduction in blood volume, for instance, and which cannot, even as a result of this hyperactivity, keep the arterial pressure up to the normal level, could effect only a relatively small additional, though, perhaps, still percentile, rise as a result of afferent stimulation.

Mann's methods of studying vasomotor tone were indirect (5). He goes further than his facts justify when he concludes that "the vasomotor center is not depressed or fatigued in shock;" his methods like those of Porter are capable of showing only that the vasomotor center possesses some degree of activity. Joseph and Seelig (24) also employed

an indirect method of following vasomotor tone. They conclude from observations on the rabbit that in shock the tone of the center is normal. But, as we interpret their results, they demonstrate merely that the center possesses some tone; they are not in a position to state what that degree of tone may be.

Muns (25) plethysmographed the leg of the dog and found that traumatizing the exposed intestines diminished the volume of the leg even when the arterial pressure remained constant. This observation is clearly indicative of a vasoconstriction in the early stage of shock production and therefore is in accord with our findings.

The methods employed by Sollmann and Pilcher (13) and by Morison and Hooker (11) are alike in that they determine the rate of flow of liquid under a constant pressure through blood vessels under the control of the vasomotor center; they, like the method of Bartlett, employed by us, are direct methods. The study of shock was only an incident in the work of Sollmann and Pilcher. In one experiment in which the arterial pressure had been reduced to 10(!) mm. Hg. by manipulation of the intestines the center failed to respond to asphyxia; it had completely lost its activity. Morison and Hooker performed six experiments upon the leg and two each upon the kidney and the intestine. It is impossible, though, to tell from their article in what stage of shock they determined the perfusion rate. They state in the text that in but one (leg) experiment the outflow was increased, and in their conclusions state that the rate of flow is decreased. One of us (8) has shown beyond peradventure that tissue abuse at once and definitively leads to a reduction in the flow of blood as measured in the salivary gland.

Finally, Wiggers (26) concludes (upon the basis of the configuration of the central arterial and intraventricular pressure curves) that from the moment the intestines are exposed and until the death of the animal the larger arteries are abnormally empty and the peripheral resistance low. Wiggers, apparently forgetful of his preliminary discussion, in which several possible explanations are narrowed down to one by a process of reasoning, by no means convincing, maintains that his evidence is a *direct* proof of the condition of the peripheral resistance, a conclusion with which we cannot agree. But, assuming for the moment that the method does indicate a diminution in peripheral resistance, it does not necessarily follow, as Wiggers himself admits, that the diminished peripheral resistance is the result of diminished central tone. The present methods have shown that early in shock production, ex-

cepting only the momentary response to manipulation of the intestines, the center, as a rule, maintains increased tone, both in the somatic area and in the parts of the splanchnic area that are not injured. We have not measured the peripheral resistance in the parts of the splanchnic area directly traumatized. According to Janeway and Ewing (27), manipulation of the intestines paralyzes the splanchnics locally, while in loops protected from exposure the vasomotor tone remains normal. This, presumably, is entirely a peripheral process. But inasmuch as the exposed loops are also the seat of an inflammatory process, it does not necessarily follow that the resistance to the flow of blood through them is diminished by the splanchnic paralysis. In the light of our direct determinations of the peripheral resistance in the early stages of intestinal exposure, it is obvious that only if the resistance were diminished in the traumatized regions would there be a way of accounting for the peculiarities of Wigger's central pressure curves on the basis of a reduction in resistance. As a matter of fact, the evidence available seems to support increased resistance to blood flow throughout the splanchnic area, rather than diminished resistance; for all investigators are agreed, as will be seen in a moment, that the portal pressure is lowered by intestinal exposure. A diminution in the resistance to blood flow in the intestinal area would have just the opposite effect.

Our experiments, as has been said, seem to indicate that in part, at least, the late loss in vasomotor tone is the result of the reduced blood flow that comes of the low pressure rather than the cause of the low arterial pressure. It is therefore conceivable that if shock could be induced more rapidly than we have succeeded in bringing it on, a low pressure might develop at a time when the tone of the center is still high. In such a case marked constriction might persist to the end.

#### *Jugular pressure*

The jugular pressure in the two experiments in which it has been followed (figs. 8, 9), varied at most 0.5 mm. Hg. Morison and Hooker (11) found that the caval pressure progressively falls; and Wiggers found that the so-called effective venous pressure falls. In shock produced by this method, therefore, the heart seems to be capable of moving on efficiently all the blood that is brought to it. This confirms the conclusion Mann (5) and others have come to on the basis of observations of another kind.



Here we may refer to a few casual observations made with the idea of testing the capabilities of the heart. In a few experiments we have from time to time determined the height to which the carotid pressure is raised when the aorta is temporarily occluded. This may be considerable even quite late in the course of the experiment, but it is not equal to that attained early in the experiment, nor is the raised pressure so well maintained. This failure of the heart in shock to equal the performance of the heart in the normal animal does not necessarily mean that the heart is at fault. For in shock the respiratory pump is apt to be feeble and the return of blood to the heart impaired.

#### *Portal pressure*

The portal pressure has been followed through one experiment and almost to the close of another. In the one complete experiment (fig. 8), upon exposure of the intestines the pressure fell from the unusually high level of 16 mm. to 7 mm. in the course of  $2\frac{1}{2}$  hours. Owing to trouble caused by clotting, the data with regard to the peripheral resistance are of but little help here in arriving at an understanding of this behavior of the portal pressure. It might, though, have been due entirely to the fall in arterial pressure. Later (after 2:00) the portal pressure rose for about  $1\frac{1}{2}$  hours; the fall in arterial pressure at this time was continuous. The inflow rate, here, is again confused by clotting; but later, when the shift was made to the other femoral artery, it was found that the peripheral resistance was diminishing. It is possible, therefore, that the rise in portal pressure which here occurs despite a falling arterial pressure, is to be explained by a giving way of the peripheral resistance. Later, the portal pressure begins to fall again and this fall is continuous to the end. Very little dilatation occurs during this last phase of the experiment. The falling arterial pressure may therefore be the cause of the fall in portal pressure.

In the other experiment (fig. 9) the behavior of the portal pressure was quite similar to that seen in the preceding case. After exposure of the intestines the pressure fell more or less steadily from 7.5 mm. Hg., reaching 5 mm. Hg. in the course of  $2\frac{1}{2}$  hours. In the presence of a constant arterial pressure this fall may fairly be attributed to the peripheral constriction indicated by the inflow readings. During the next 3 hours the portal pressure was practically stationary. In the same period the arterial pressure for the most part was falling, while the inflow readings were quite variable; so much so that the data furnish no clear basis for the interpretation of the behavior of the portal pressure.

Our finding that exposure of the intestines, upon the whole, lowers the portal pressure, confirms Morison and Hooker (11), in most of whose experiments the animal was merely kept on the table under an anesthetic until the arterial pressure fell.

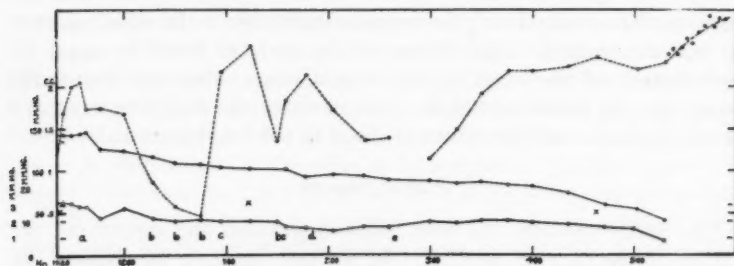


Fig. 8. Experiment 58. Shock by exposure and manipulation of the intestines. Arterial pressure, —●—; femoral inflow, ····●···; portal pressure, —○—; jugular pressure, X X. a, intestines exposed; b, partial clot in inflow cannula; c, clot removed; d, accidental injection of carbonate, respiration stopped but recovered in 8 minutes; e, changed to other femoral artery.

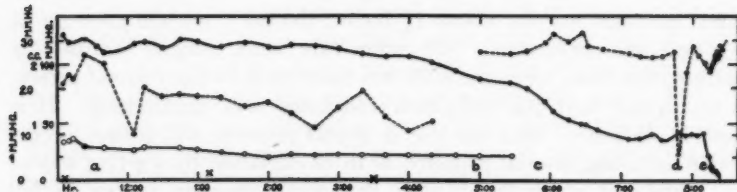


Fig. 9. Experiment 59. Exposure and manipulation of the intestines. Arterial pressure, —●—; femoral inflow, ····●···; portal pressure, —○—; jugular pressure, X X. a, abdomen opened; b, changed to other femoral artery; c, abdomen opened wider; d, injected strong carbonate; e, heart stabbed.

### Inspection

In experiments of this kind one gains the impression that the larger veins of the splanchnic area do not contain more blood when the animal is in shock than when the intestines are first exposed. It is realized, however, that this method of estimating venous engorgement is too subjective to be of any great value, as is evidenced by the conflicting opinions of different observers.

When the intestines are first exposed, the peritoneum covering them is perfectly smooth and glistening. In time, however, fine beads begin to form on it; these run together forming larger beads and eventually the fluid so formed streams off the bowels in considerable amounts. In several experiments, by placing the bowels on a tilted glass plate, the larger part of the fluid thus exuding was collected over definite periods. At times it dripped away at the rate of over 1 cc. per minute. The total amount formed probably never has exceeded 150 cc. This weeping of the peritoneal surface probably accounts in part for the concentration of the blood that occurs in this type of shock. The bowels also become boggy to the touch as though they were edematous. A certain amount of fluid must be abstracted from the circulation by this process also.

At post-mortem examination, petechial hemorrhages into the serosa are not uncommonly found. The mucosa of the intestines is deeply congested, of a deep, bluish-red color and the lumen of the bowel may contain some bloody material. On microscopical examination there is found relatively little hemorrhage into the mucosa. But the capillaries and the veins of the villi are tremendously distended with solid columns of corpuscles. It is undoubtedly this that gives the mucosa its deep red color, rather than the hemorrhage.

### *Summary*

The immediate effect of exposure of the intestines usually is a vasoconstriction, often of a moderate grade (as compared with some other shock-producing procedures to be described later) affecting both the somatic and the splanchnic areas, with the possible exception of the parts directly traumatized; a fall or no change in the arterial pressure; a fall in portal pressure; and a slight, probably unimportant, change in the pressure in the right auricle. In view of the fact that the energy of the heart at this time is not reduced, this combination of effects seems to be accounted for best upon the basis of a reduction in effective blood volume; possibly also upon the basis of a dilatation in the traumatized region. The fact, however, that the portal pressure falls seems to exclude the latter, and to lend support to the view either that constriction is occurring in the traumatized area as well as elsewhere, or that exposure of the intestines mechanically interferes with the emptying of the veins of the splanchnic area, or that the distention of the splanchnic capillaries and venules with masses of corpuscles blocks

the entrance of blood into the portal area. Weeping from the serous surface of the injured viscera must tend toward reducing the blood volume.

The later consequences of exposure of the intestines are: continuation of the fall in arterial pressure; eventual diminution in vasomotor tone; and a slight rise, or a cessation of the fall, of the portal pressure. The absence of constriction, indeed, the development of an actual dilatation in the face of a low arterial pressure bespeaks a giving way of the vasomotor center. This giving way, presumably, is largely a reaction on the part of the center to the long-continued unfavorable conditions, among which must be included the low arterial pressure. The vasoconstrictor center, though, preserves a certain amount of tone and of reactivity to the end. The capillaries and veins of the villi of the intestines are greatly distended with blood.

#### SHOCK IN ANIMALS DEPRIVED OF SYMPATHETIC CONTROL<sup>1</sup>

Reflex inhibition of the tone of the vasoconstrictor center, affecting the splanchnic area in particular, may be regarded as one of the earliest of the hypotheses of shock founded upon experimental observation. If reflex inhibition of the constrictor center is the cause of the shock that results after exposure and manipulation of the intestines, it was felt that it should be more difficult to bring on shock in animals so prepared that there would remain but little opportunity for the play of such reflexes. It also has been maintained that shock is due to constriction of the portal radicles in the liver with consequent damming back of blood in the portal area.

A number of methods are available of putting these views to the test of experiment. One that we employed consisted in studying shock-producing procedures in animals after cutting the splanchnic nerves and removing the abdominal sympathetic chain. In this way the sympathetic connection of the abdominal viscera with the central nervous system is severed and the possibility of vasoconstrictor reflexes to them, to the parietal peritoneum, as well as to a large part of the soma, is excluded.

Two animals survived this rather difficult operation long enough for the immediate effects to wear off. Several weeks later the effects of traumatization were studied. The initial arterial pressures of these

<sup>1</sup> These experiments were done by one of us (H. S. G.) with the assistance of B. Landis Elliott.

animals were 80 and 100 mm. Hg.—not as low as was anticipated in the absence of the central vasoconstrictor control of practically all of the vessels below the level of the diaphragm.

*Experiment 22.* In this experiment, the data of which are collected in figure 10, the arterial pressure was falling when the registration of the pressure was begun, and by the time the abdomen was opened it had already practically reached the level of 50 mm. Hg. The fall in arterial pressure ("shock"), therefore, can scarcely be attributed in this case to the exposure of the intestines. Excepting possibly a slight increase early in the experiment and one aberrant reading, the inflow rate, followed in both the right and left femoral arteries, remained prac-

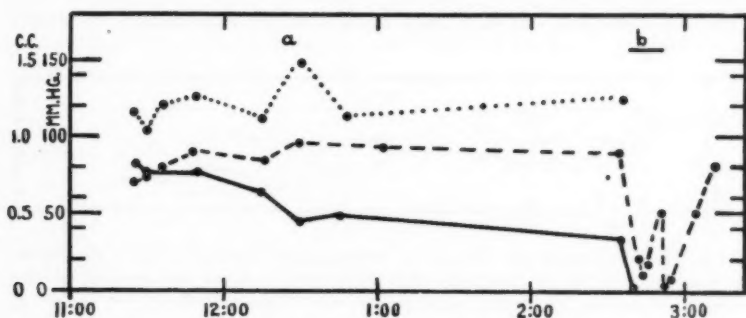


Fig. 10. Experiment 22. Shock after excision of abdominal sympathetic chain and section of the splanchnic nerves. Arterial pressure, —•—•—; right femoral inflow, .....; left femoral inflow, —•—•—; a, abdomen opened; b, adrenalin injected.

tically constant through shock and death. Evidently the preliminary operation had accomplished its end.

*Experiment 26 (fig. 11).* A pressure of 50 mm. Hg. was reached in something over  $2\frac{1}{2}$  hours after opening the abdomen, and the animal died about  $3\frac{1}{2}$  hours later. Early in the experiment each manipulation of the intestines (b, fig. 11) caused the arterial pressure to fall and the femoral vessels to dilate. This reaction presumably was mediated through the vasodilator mechanism; for the femoral area, the area in which the state of tone was followed, was isolated from the vasoconstrictor center by the preliminary operation. The afferent path of this reflex must, therefore, have been by way of the visceral fibers of the vagus nerve (28). Excepting these fluctuations, the inflow rate was

never, not even after death, more than 0.2 cc. per minute above or below a rate of 1.6 cc. per minute. Manipulation of the intestines in this case obviously hurried the animal into shock.

These two experiments prove that the preliminary operation had accomplished its object of freeing the lower parts of the body from vasoconstrictor influences. The level of 50 mm. Hg. was reached in one (exp. 22) about 1 hour after starting the record; in the other, in something less than 3 hours. Shock, therefore, developed faster in these animals than in any other of the animals in which it was induced by exposure of the intestines. The explanation of this fact may lie either in the rundown condition of the animals at the time they were experimented upon, or in the liberation of a large part of the body from vasoconstrictor control. If the latter is the correct explanation, it would

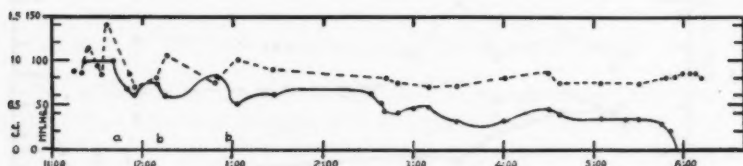


Fig. 11. Experiment 23. Shock by exposure and manipulation of the intestines after excision of the abdominal sympathetic chain and section of the splanchnic nerves. Arterial pressure, —•—; femoral inflow, ·····. a, abdomen opened; b, b, intestines manipulated.

constitute a reason for believing that the vasoconstriction usually present in the earlier stages of shock development in the case of undenervated animals is, as we have every reason for believing, an effort at compensation of something that is tending to lower the arterial pressure.

Furthermore, if the shock that is induced by exposure and manipulation of the intestines is due to the accumulation of blood in the splanchnic area, these experiments would serve to indicate that the accumulation is not attributable to the trapping of blood in the portal area through constriction (29), nor to a dilatation that comes about through loss of vasoconstrictor tone. The increased capacity of the peripheral vessels must develop either through the action of some *local* mechanism or through continuous central vasodilator stimulation. The latter alternative, to say the least, is highly improbable.



## SHOCK IN EVISCERATED ANIMALS

Three animals have been followed through shock after removing the stomach, intestines and spleen. The operation was performed in such a way as to carry away with these organs a minimum of blood. The results in all three experiments were essentially alike (see fig. 12). The arterial pressure was well maintained for a while and then fell gradually, reaching the 50 mm. Hg. level in 3, 4 and 6 hours, respectively. Evisceration was always followed by a reduction in the femoral inflow lasting as long as 2 or more hours; in the case used here for purposes of illustration the constriction was the least marked and the most transient of all. At about the time the arterial pressure begins to fall rapidly, vasoconstrictor tone begins to give way and it becomes subnormal long before the animal dies. Death has occurred in from 4½ to 7 hours.

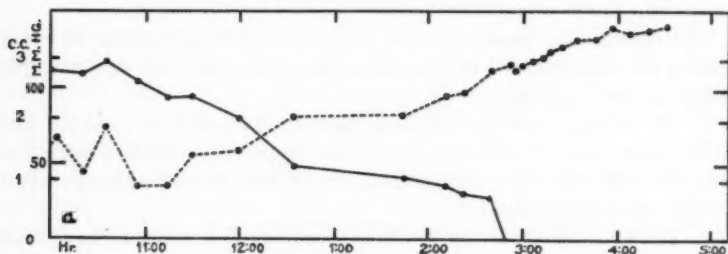


Fig. 12. Experiment 17. Failure of the circulation after evisceration. Arterial pressure, —•—; femoral inflow, .... At a, the stomach, intestines and spleen were excised.

*Discussion.* These experiments were performed with the idea of testing the view, widely held, that the splanchnic area is primarily the location in which are enacted the events that lead to shock. This rôle has been assigned at various times to such processes as the accumulation of blood in the splanchnic and portal capillaries and veins due to splanchnic dilatation, the damming back of blood in the portal area as a result of an increase in hepatic resistance, loss of tone in the portal system, loss of blood "due to the reaction of the great delicate vascular splanchnic area to irritation—an acute inflammation of the peritoneum," (5), etc., etc. Some investigators have gone so far as to maintain that shock can be produced in animals solely by exposure and manipulation of the intestines.

The present experiments demonstrate not only that typical shock develops in animals in which none of these mechanisms has a chance to work, but in addition, that the vasomotor reactions and the duration of the several stages of shock development (see table 1) are essentially the same in the eviscerated as in the uneviscerated animal. Indeed, the vasoconstriction of the early stages of shock induction is more marked in the former even than in the latter. We do not wish to give the impression that exposure and manipulation of the viscera are not factors in the development of shock; the present experiments merely demonstrate that after the animal has been started on its way to shock, partly perhaps through the handling of the viscera that evisceration entails, none of the above-mentioned mechanisms is needed to hurry the animal along its downward course.

#### SUMMARY AND CONCLUSIONS

The changes in the circulation found in this investigation to occur during the development of shock brought on by exposure and manipulation of the intestines are as follows:

1. The arterial pressure at first may be lowered but little, if any. After some time, it may be after some hours, the pressure begins to fall, and this fall then continues more or less steadily, though often slowly, until the animal dies.
2. The changes occurring in the systemic venous pressure have been so small that they cannot be regarded as significant, excepting, perhaps, in demonstrating that cardiac failure has little, if anything, to do with the failure of the circulation.
3. The portal venous pressure falls continuously, though slowly, during the first 2 to 3 hours. It then ceases to fall or actually rises slightly until the arterial pressure has reached a comparatively low level, when the portal pressure again begins to decline.
4. The peripheral resistance, both somatic and splanchnic, at first practically invariably is increased. At about the time the arterial pressure begins to fall, or starts on its steady decline, and also at about the time the portal pressure starts to rise, the peripheral resistance begins to diminish and by the time the arterial pressure has reached the vicinity of 50 mm. Hg., the peripheral resistance practically invariably is below normal. But up to the time of death the vessels preserve some residual tone and the vasomotor center some, though slight, reactivity. In this respect the findings of Bartlett (9) are completely confirmed.

5. A considerable loss of fluid from the exposed bowel occurs as a result of transudation through the serous surface, and presumably into the tissues also. The capillaries and veins of the intestinal villi are greatly distended and tightly packed with red corpuscles.

6. No positive evidence has been obtained that the efficiency of the heart is impaired during the development of shock. Nevertheless, although the heart is capable of raising the arterial pressure as high as can the normal heart, we are inclined to believe that the heart in shock cannot maintain high pressures as long as can the normal heart.

7. The initial changes in the circulation can be explained best upon the assumption that the effective blood volume is reduced.

The loss of fluid into and through the tissues of the bowel and the sequestration of blood in the intestinal capillaries and venules suggest a mechanism through which a reduction in blood volume might occur.

But if this is the mechanism, the fact that after excision of the stomach, intestines and spleen the arterial pressure falls almost exactly in the same way as after exposure of and manipulation of the intestines, and the fact that the changes in peripheral resistance are also alike, necessitate assuming that blood is thus removed from circulation, not alone in the parts of the body directly traumatized, but elsewhere also.

It is impossible to determine, on the basis of the present experiments, what rôle, if any, the preliminary constriction plays in the subsequent failure of the circulation. But the experiments in which, by excision of the abdominal sympathetic chain and section of the splanchnic nerves, the entire posterior half of the body was removed from vasoconstrictor control, indicate, as might have been anticipated, that vasoconstriction is not essential to the development of a shock-like failure of the circulation.

Although at first the vasomotor center, as a rule, strives, by increasing the peripheral resistance, to compensate the processes that are tending to lower the arterial pressure, the reactivity of this center becomes subnormal long before the arterial pressure has fallen to the level of 50 mm. Hg.; this ultimate failure of the center to respond with a *strong* constriction to the stimulus of a low arterial pressure must be regarded as a secondary factor in the development of the low arterial pressure in this type of shock.

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# PROCEEDINGS OF THE AMERICAN PHYSIOLOGICAL SOCIETY

THIRTY-FIRST ANNUAL MEETING

Johns Hopkins University, Baltimore, April, 24, 25, 26, 1919

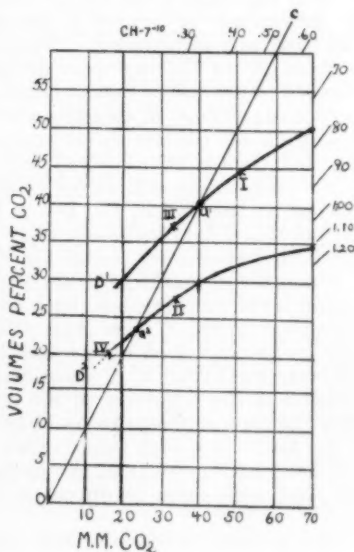
## IN MEMORIAM

Admont Halsey Clark  
Ralph Edmond Sheldon  
Frank Fairchild Westbrook

*The CO<sub>2</sub> dissociation curve as the complete expression of the acid base equilibrium of the blood.* YANDELL HENDERSON and HOWARD W. HAGGARD.

In studying some problems of asphyxia and acidosis, we had occasion to plot a series of CO<sub>2</sub> dissociation curves. The data were from the blood of a dog which had received increasing amounts of HCl intravenously; and we made the following observation. With increasing dosage of acid and neutralization of the NaHCO<sub>3</sub> of the blood, the curves came to progressively lower levels. At the same time the points in the curves corresponding to the arterial blood, (the points A1 to A4 in the figure) fell further and further to the left. Furthermore when these arterial points were connected they were found all to lie on or close to a diagonal straight line, and this line when continued passed through the intersection of ordinate and abscissa.

Consideration of these graphic relations shows that such a line expresses the same C<sub>H</sub> at every point throughout its length, for all points in it indicate the same ratio of dissolved CO<sub>2</sub> to combined CO<sub>2</sub>. We term it the O-C line, or line of C



values. It expressed the inherent sensitiveness of the respiratory center to its chemical control. It demonstrates that the  $C_H$  and not the total  $CO_2$  in the blood (i.e., not the concentration of  $HCO_3$  ions) is the hormone of respiration. It enables us to modify the Haldane-Priestley law of respiration thus: The volume of the pulmonary ventilation varies inversely as the amount of alkali which in the condition of the blood at the time will afford the normal  $C_H$ . In other words, normal respiration adjusts the tension and content of  $CO_2$ , i.e., alkaline reserve, in the arterial blood to values corresponding to the point of intersection of the dissociation curve, whether high or low, with the O-C line.

Study of the  $CO_2$  diagrams of many types of experiment shows that instead of merely two possible abnormal conditions, acidosis and alkalosis, there are theoretically four: *a*, high  $NaHCO_3$  and high  $C_H$ ; *b*, low  $NaHCO_3$  and high  $C_H$ ; *c*, high  $NaHCO_3$  and low  $C_H$ ; and *d*, low  $NaHCO_3$  and low  $C_H$ . Regarding these four conditions, *a* probably occurs only in morphin poisoning and related conditions; *b* is the condition now termed uncompensated acidosis; *c* is perhaps what is now termed alkalosis; *d* is a condition which has not heretofore been distinguished from *b*. In its nature and proper mode of treatment *d* is however profoundly different from *b*. (The  $C_H$  scale given in the figure is merely illustrative).

*Studies on the responses of the circulation to low oxygen tension. I.*

*Types of variation in blood pressure and heart rate.* CHAS. W. GREENE.

Schneider<sup>1</sup> has established the general type of compensation made by men undergoing the Air Service test to low oxygen tension in which the percentage of oxygen is gradually decreased during rebreathing. The heart rate is increased. The acceleration is slight at first beginning at from 16 to 12.2 per cent oxygen and growing more and more pronounced to the end of human endurance. The total increase may reach forty beats or more in an adequate reactor. In the ideal type systolic pressure holds till late in the test, till the oxygen is lowered to 14 to 9 per cent, then gives a gradual rise. The diastolic holds or rises slightly in the early stage and shows a fall at the low oxygen level often very marked at the end of the test. These are Schneider's types and he has published data including type charts in the Manual of the Medical Research Laboratory of the Air Service, War Department, 1918.

A number of marked variations from the types are selected and presented here for discussion, both from the cardiac group and from the vasomotor group. These types indicate that vascular compensation may be accomplished by a number of variations from the type. The following are listed: *a*, A sharp increase both in heart rate and systolic pressure at the beginning of the test, which hold at the new level and show the typical heart rate and blood pressure compensations to the end of the test. *b*, A high initial blood pressure response that holds on the new level with more than the average increase in the late stage of the test, but with slight compensation in heart rate. *c*, The converse of

<sup>1</sup> Journ. Amer. Med. Assoc., 1918, lxxi, pp. 1382-1400.



type *b*, a great increase in heart rate beginning early in the test and progressing to the end but coupled with little or no systolic compensation and often with early diastolic fall. *d*, Unusually high systolic pressures that fail in compensation and tend to collapse. The possible significance of these types is discussed.

*Variations in alveolar air at low pressures.* BRENTON R. LUTZ.

A preliminary report of twenty-four cases in which the alveolar air tensions were determined under conditions of rapid reduction of atmospheric pressure is presented. Reduced barometric pressures were produced in one of the low pressure chambers at the United States Army Medical Research Laboratory, Mineola, L. I., N. Y., at a rate simulating an air-plane ascent, that is, 352 mm. Hg. or 20,000 feet were attained in twenty minutes. Alveolar air samples were taken in Henderson alveolar air sampling tubes after the expiratory method of Haldane and Priestley. These were analyzed for oxygen and carbon dioxide with a Henderson-Orsat gas analyzer. Samples were obtained at sea level, 4,000 feet, 8,000 feet, 12,000 feet, 16,000 feet and 20,000 feet.

The average curve for oxygen and carbon dioxide shows a fall present at the fourth minute and continuing until the ascent was completed. The average sea level values were 103 mm. Hg. for oxygen and 39.6 mm. Hg. for carbon dioxide. The average values at 4,000 feet were 83.7 mm. for oxygen and 37.0 mm. for carbon dioxide; for 8000 feet, 66 mm. and 36 mm. respectively; for 12,000 feet, 53.2 mm. and 33.5 mm.; for 16,000 feet, 42.6 mm. and 31.3 mm.; for 20,000 feet, 34.8 mm. and 30 mm. These twenty-four cases indicate that in an ascent at the rate of 1000 feet a minute both the alveolar oxygen tension and the alveolar carbon dioxide tension begin to fall very early, reaching at 20,000 feet, 34.8 mm. Hg. for oxygen and 30 mm. Hg. for carbon dioxide.

*Variations in respiration volume and oxygen consumption during the reduction of the oxygen tension and during short exposures at the reduced oxygen level.* MAX M. ELLIS.

The changes in respiration volume and oxygen consumption of men at sea level, during the reduction of oxygen and during the first ten minutes at the new level of reduced oxygen, were obtained from a rebreather containing 54 litres of air. The carbon dioxide produced by the subject was removed by a potassium hydroxid cartridge.

The general response in volume was an increase in the per minute volume, as compared with the sea level volume, during the reduction of oxygen, followed by a decrease in the volume moved while at the new level of reduced oxygen. The per minute volume at the reduced oxygen level remained consistently higher than the sea level volume. The increase in volume moved was initiated in most cases before 17.5 per cent oxygen was attained.

The general response in oxygen consumption was the same as that in volume, a rise in the per minute oxygen consumption above the sea level

value during the reduction of oxygen, followed by a fall in the per minute consumption at the new level of reduced oxygen. The value at the reduced oxygen level was higher in the majority of cases than the sea level value.

The responses were more profound in subjects carried to equivalent altitudes above 10,000 feet.

*Phenomena following indirect concussion of the skull.* T. S. GITHENS and S. J. MELTZER.

Concussion was produced in completely etherized dogs by a weight falling on a board 4 cm. thick laid on the head in front of the occiput. Complete unconsciousness continued till the end of the experiment.

We wish to report briefly the following phenomena which were observed.

*Brain.* The lid and corneal reflexes were never lost. The eyes showed nystagmus for an hour or so after the concussion and afterward were moved in an apparently normal manner. Stimulation of exposed sensory nerves (e.g., supra-orbital) caused no sign of pain and no influence on respiration or other reflex effect even after four hours. A new nose-licking reflex was noted. If the nasal septum were pinched by forceps, no response occurred during the pressure, but on releasing it the tongue was protruded and licked the nose. This was seen in all the dogs in which it was systematically looked for.

*Medulla.* The medullary centers were surprisingly little affected. The blood pressure was usually very high soon after the concussion, and the respiration was noisy and irregular, soon becoming normal. Section of the vagus nerves interfered with respiration as in decerebrate animals. After section of one vagus, stimulation of the central end caused active expiration or expiratory stoppage.

*Cord.* For the first hour or so there was complete paralysis with loss of all reflexes and responses. Later, circulatory, respiratory and spinal reflexes returned and often became exaggerated. Many of the dogs showed a generalized tremor beginning within an hour and lasting until the animal was killed several hours or even a day later. In three dogs there was some indication of returning pain sense after two or three hours. Stimulation of the sciatic nerve after return of reflexes caused stiffness of one or more legs, often associated with emprostotonos of the abdominal region and opisthotonos of the cervical; the pelvis being drawn forward and the head backward. Similar phenomena were obtained from stimulation of the brachial plexus. The muscles of the head itself were never involved. Stimulation of the cervical nerves never caused any response except active expiration.

*Lesions.* Only gross study of hemorrhage was made. The only characteristic lesion was a hemorrhage into the upper part of the cord extending from the calamus to the second or third cervical nerves. This was associated with laceration of the gray matter extending from the central canal into the dorsal horns. There was almost no hemorrhage within the skull.

*Physiological effects of air concussion.* D. R. HOOKEP.

Through the assistance of the National Research Council and the coöperation of the Ordnance Department of the Army, facilities were obtained for the study of the physiological effects of air concussion in animals. For the most part, anesthetized dogs were used. They were exposed at varying distances in front of large calibre rifles and if the concussion pressure amounted to approximately twenty atmospheres, a shock-like result was obtained, i.e., the arterial pressure fell immediately (five minutes) from a control value of 100-150 mm. Hg. to 40-60 mm. Hg.

After this condition was established, the animals remained alive for one to ten hours and efforts were directed to a study of some of the concomitant phenomena. Both the pulse and respiration were accelerated presumably as the result of the lowered arterial pressure. In a single case the blood catalase was not reduced. The alkaline reserve was normal immediately after exposure but fell markedly in the course of an hour. No air bubbles could be found in the vascular system nor was there evidence of intravascular fat sufficient to account for the results. The medullary reflexes, so far as tested, were all normal. That is to say, respiratory, cardiac and vasomotor responses were readily elicited upon sensory nerve stimulation. The eye-lid reflex was active.

The most interesting result was found in the venous side of the circulation. The venous pressure invariably showed a fall. This pressure was down immediately after exposure and continued subnormal until death, an observation which suggests, in view of the efficiency of the vasomotor mechanism, an inadequate venous filling as a causative phenomenon of the condition. This suggestion is strengthened by the appearance of the abdominal veins. If examined late in the condition, the veins were small, dark and relatively inconspicuous. If examined shortly after exposure, they were obviously very much enlarged. The fact that this enlargement of the abdominal veins accompanied a low venous pressure may be interpreted as indicating a failure of the venopressor mechanism. The late appearance of the veins, according with clinical observation, is doubtless due to transudation of blood plasma.

The sole pathological lesion found was a scattered hemorrhagic condition of the lungs, as has been noted by Crile. It is conceivable that this tissue injury released a toxic substance adequate to establish shock. But the extent of injury did not run parallel with the symptoms; in fact, many animals with an extreme grade of pulmonary involvement failed to show circulatory collapse.

*On the general expression of the law of cicatrization of wounds.* P. LECOMTE DU NOÛY.

The cicatrization of surface wounds is a phenomenon which is likely to involve quite a great number of elementary phenomena. But as all the latter are related to each other by definite, although unknown, laws, it seemed that the resulting phenomenon, cicatrization, could be studied in the same way as the ordinary physico-chemical phenomena, in order

to see whether a general law could be assumed. To comply with this purpose, a technique had to be developed for measuring accurately the area of wounds. Sterilized cellophane was applied to the wound, and the edge was outlined with a wax pencil. This drawing was transferred in ink to an ordinary sheet of paper, and the area was measured by means of a planimeter. A curve was obtained by carrying the area, in square centimeters, in ordinates, and the time, in days, in abscissae. A great number of experiments on animals and on human beings during the war, brought forward a great number of interesting facts, which we shall try to review rapidly.

At first it was shown that the cicatrization of a wound was due to two different factors: contraction and epithelization, the first one being the most important.<sup>1</sup> When the wound is kept aseptic, the curve representing the cicatrization plotted as above said is perfectly geometric, and can be expressed by a mathematical formula. In this formula enters a certain coefficient, which we called "i," or index of cicatrization, which is inversely proportional to the age of the patient or of the animal. This means that by making one single measure of the area of the wound, and provided the age of the patient is known, one can draw the curve representing the normal healing of a wound.<sup>2</sup> Beside its scientific interest, this has many practical advantages. First: It allows the physician to compute the total time which is necessary for the wound to heal. Second: It gives indications as to the "physiological age of the patient" which, indicated by his own curve, may differ from his real age. Third: When it has been proved that a wound heals normally, comparison between the calculated and the observed curve will indicate the real value of the substance which is used on the dressing.<sup>3</sup>

This latter technique has been extensively used during the war to ascertain the action of antiseptics. It was found that most of them were irritating and interfered more or less with the normal process of cicatrization. Having a daily witness, a standard curve, to which the observed curve was always compared, it was a very easy and rapid work to determine the value of the so-called "cicatrizing substances." We found that no such thing exists so far. The ideal condition of perfect and most rapid healing is realized when the wound is kept practically sterile, or deprived of pathogenic microbes such as cocci, diplococci, streptococci and so forth. These conditions were realized with the Carrel method.

*A device for injecting fluids intravenously.* P. LECOMTE DU NOÛY.

This device does away with piston, gears and valves. The only part which has to be sterilized is the piece of rubber tubing which is used with the needle. It aspirates and compresses, up to 30 or 35 cm. of mercury. It is controlled either by hand or by motor, and the flow may be regulated from 2 or 3 cc. a minute, or less, up to 50 cc. and more.

<sup>1</sup> Carrel and A. Hartmann: Journ. Exper. Med., November 1, 1916.

<sup>2</sup> du Noüy: Journ. Exper. Med., November, 1916; May, 1916; April, 1919.

<sup>3</sup> Carrel, du Noüy, Carrel: Journ. Exper. Med., August, 1917.

See also: Tuffier and Desmarres: Journ. Exper. Med., February, 1918.

*A new form of the Mohr's specific gravity balance for small quantities of liquids.* P. LECOMTE DU NOÛY.

This balance gives the  $\frac{1}{10}$  of a milligram by the means of a rider. The plunger being about 1 cc., the numbers read on the weights indicate the density of the liquid tested, if the apparatus has first been standardized with water.

*An apparatus for measuring rapidly and accurately the surface tension of all liquids.* P. LECOMTE DU NOÛY.

It is based upon the well-known adhesion principle, of a disc or ring or square, brought into contact with the liquid. The tension is measured by the torsion of a wire, which torsion is simply read on a dial.

*The behavior of the centriole and the centrosphere in the degenerating fibroblasts of tissue cultures.* WARREN H. LEWIS.

In the normal healthy fibroblast the centriole lies close to one side or one end of the nucleus. The mitochondria do not appear to have any definite relation to it since they are arranged more or less parallel to the long axis of the cell. A few scattered granules are usually present. As degeneration progresses the granules increase in number and tend to accumulate about the centriole. As the process goes on the accumulation of granules about the centriole increases and each granule usually becomes surrounded by a vacuole.

Coincident with this accumulation of granules, the mitochondrial threads and rods become more or less radially arranged about the centriole. As the number of vacuoles and granules increases there develops about the centriole a clear area, the centrosphere, which gradually increases in size and may become as large as the nucleus. The centrosphere is usually quite free from granules, vacuoles and mitochondria. Protoplasmic strands, in which the mitochondria lie, extend from the centrosphere toward the periphery and often give a radial arrangement as the vacuoles. As degeneration proceeds the mitochondrial threads often break up into short rods and granules which may change into vesicles.

The small degeneration vacuoles and granules often exhibit quite active movements different from and more extended than the ordinary mitochondrial movements. The direction is from the region of the centriole or centrosphere to the periphery of the cell or *vice versa*. Are such movements due to cytoplasmic currents or to the metabolic interchanges between vacuoles or granules and the cytoplasm?

The orientation of the various structures about the centriole and centrosphere in degenerating fibroblasts suggests that the centriole and not the nucleus is the center of metabolic activity of the cell, the dynamic center of the cell according to Boveri.

This increase in the size of the centrosphere is probably a compensating reaction on the part of the cell induced by an upset in the normal metabolic balance between centriole and periphery through the accumulation of granules and vacuoles.



*A comparison of the influence of secretine and the antineuritic vitamine on pancreatic secretion and bile flow.* CARL VOEGTLIN and C. N. MYERS.

An alcoholic extract of dried brewers' yeast, after being submitted to the same purification as described for the preparation of Funk's vitamine fraction, causes, when injected intravenously, a marked increase in pancreatic secretion and bile flow. Extracts of the mucosa of the duodenum prepared in the same manner still possess their characteristic action on pancreatic secretion and also relieve the paralytic symptoms of polyneuritic pigeons.

Later experiments by Voegtlin have furthermore shown that liver, heart muscle and milk also contain a substance which stimulates pancreatic secretion and increases the flow of bile. The presence of the antineuritic vitamine in such extracts had been previously demonstrated. Hence it is concluded that secretine is not only located in the intestinal mucosa, but also in at least two other organs of the body.

The failure of previous workers to extract secretine from these organs is probably due to the use of improper chemical methods.

From these and other observations it is concluded that secretine and the antineuritic vitamine are very closely related, if not identical.

*Electric conductivity in relation to shock and exhaustion.* GEORGE W. CRILE and HELEN R. HOSMER.

In previous researches histologic and clinical findings have indicated that in exhaustion and shock there exists an apparent synthetic relationship between certain organs—notably the central nervous system and the liver. The work of Lillie, Osterhaut and Galleotti and other biophysical chemists suggests that further evidence of the rôle of these organs in exhaustion and shock might be secured by measurements of their electric conductivity.

The research of which this paper presents a preliminary report was therefore undertaken, the first measurements being made by Capt. G. B. Obeart of the Case School of Applied Science, and the work continued by Miss Helen R. Hosmer.

Electric conductivity measurements of 107 rabbits have been made. This number includes 24 normal rabbits and groups of at least 6 rabbits, each of which were subjected to exhaustion from each of the following causes: prolonged insomnia, surgical shock, fright, infection, adrenalin injection, thyroid feeding, hydrochloric acid injection. We have studied also the effect of sleep and rest for different periods, of morphin alone and in the presence of infection, of prolonged ether anesthesia, of prolonged nitrous oxid-oxygen anesthesia.

These preliminary studies, *a*, have shown consistent antithetic changes in the brain and the liver; i.e., in every type of exhaustion the electric conductivity of the brain was decreased below the normal and the conductivity of the liver was increased above the normal; *b*, have indicated a general range of electric conductivity of the various organs and tissues.



In general, like changes under the same conditions were observed in the cerebrum and the cerebellum—these changes being most marked in the cerebellum. This finding is consistent with our observations of the comparative histologic changes in the cerebrum and cerebellum produced by exhaustion from the same causes.

*The dependence of respiratory activity upon conditions in the central mechanism.* F. H. PIKE, HELEN C. COOMBS and A. BAIRD HASTINGS.

While respiratory activity may be automatic under certain conditions,<sup>1</sup> it is almost certainly not wholly automatic under the ordinary conditions of life. Afferent nerve impulses affect not only the frequency of the respiratory movements, but also their form. In this latter function the vagus and the afferent roots of the spinal nerves enter into the problem. We strongly support Baglioni's<sup>2</sup> contention on this point. The functional relation of the dorsal roots of the thoracic nerves to the efferent roots to the intercostal muscles may be regarded as merely a special phase of the wider functional relations of afferent to efferent roots as set forth by Sherrington. We have shown that strychnine convulsions of the respiratory muscles fail after section of the dorsal roots of the thoracic nerves, just as they fail in the skeletal muscles generally after section of the afferent spinal root.<sup>3</sup>

Other factors, generally considered to be related to the concentration of the hydrogen ions in the circulating blood, enter into the problem. The regulation of the respiration becomes at bottom a problem of the conditions and manner of stimulation of the nervous elements of the central respiratory mechanism. It has been shown<sup>4</sup> that restriction of the volume of blood flowing through the medulla oblongata increases the minute volume of the respiration. We have shown that there is also a reduction in the total carbon dioxide of the blood plasma. Hyperpnoea, or even dyspnoea, follows partial or complete occlusion of the four cerebral arteries in the cat, and the concentration of the carbon dioxide in the plasma falls rapidly. Restoration of the cerebral circulation is followed by a prompt cessation of the hyperpnoea and a rise in the carbon dioxide of the plasma.<sup>5</sup>

The changes in respiration on partial or complete occlusion of the cerebral arteries are opposite in direction to what one would expect if the change in the concentration of carbon dioxide and the related change in the concentration of the hydrogen ions were the only factors concerned. We can see no obvious source of large quantities of acid in these experiments, and we are not convinced that a low concentration of carbon dioxide in the blood is an unfailing indication of acidosis.

<sup>1</sup> MacDonald and Ried: Journ. Physiology, 1898, xxiii, 100; Stewart and Pike: This Journal, 1907, xix, 328; Winterstein: Arch. f. d. gesamt. Physiol., cxxxviii, 159.

<sup>2</sup> Baglioni: Zur Analyse der Reflexfunction, Wiesbaden, 1907.

<sup>3</sup> Moore and Oertel: This Journal, 1899, iii, 45.

<sup>4</sup> Geppert and Zuntz: Arch. f. d. gesamt. Physiol., 1888, xlii, 218.

<sup>5</sup> Proc. Soc. Exper. Biol. and Med., 1919, xvi, 49.

A consideration of our experimental data leads us to the conclusion that it is not merely the condition in the circulating blood, which Haldane emphasized, but also the set of conditions in the medulla oblongata itself, dependent upon at least four different factors, which determines the degree of respiratory activity. It is our present view that respiratory activity is regulated in such a way as to maintain the usual or normal set of conditions as nearly constant as possible. The activity of the respiratory mechanism during the restriction of blood flow through the medulla is independent of any known antecedent change in the group of afferent nerve impulses and, to this extent, is automatic. But in the normal action of the central mechanism of respiration, there is a summation of all the various forms of stimulation, chemical and nervous, by the nerve cells present therein.

*Observations on decerebrate cats.* LOIS FRASER, R. S. LANG and J. J. R. MACLEOD.

It has been shown by one of us that the respiratory volume remains fairly uniform for three or four hours in most decerebrate cats after the effects of the initial etherization have passed off. Hyperpnoea usually develops later and this is accompanied by a depression in the alveolar  $\text{CO}_2$  percentage and a lowering of the arterial blood carbonate. In the present investigation it was intended to study the effect produced by causing the animal to breathe through valves into a closed system of wide-bore tubing provided with soda-lime absorption bottles and a Gadow-Krogh spirometer. The object was to find the exact degree of oxygen deficiency at which increased pulmonary ventilation would supervene, and to seek for evidence as to whether this hyperpnoea is associated with changes in the alveolar air (R.Q.) and blood (arterial-blood  $\text{CO}_2 + \text{PH}$ ) that could be attributed to the appearance in the organism of unoxidized acid.

Although a sufficient number of data has not as yet been collected to answer these questions, the interesting observation has been made that a decided hyperpnoea develops a few minutes after connecting the animal with the respiration tube and spirometer. The evidence of this hyperpnoea is obtained partly by observing the tracing produced by the spirometer, or by a tambour connected with the tracheal tube before the valves, and partly by analysis of the alveolar air. The results with the latter have invariably shown a decrease in the percentage of  $\text{CO}_2$  and a decided rise in the respiratory quotient, while the oxygen in the inspired air is still well above 15 per cent.

Similar results were obtained in two experiments in which an excess of oxygen was added to the system before causing the animal to respire into it. There can be no doubt that the slight resistance offered to expiration has served to increase the excitability of the respiratory center. This may be due to afferent stimuli set up either by the more distended condition of the alveoli (acting on the center through the vagi) or by the distended condition of the thoracic walls (acting through the muscle nerves). The following figures will serve to illustrate the results.

NUMBER OF EXPERIMENT	RESPIRATORY VOLUME IN CUBIC CENTIMETERS PER MINUTE		RESPIRATORY QUOTIENT		O <sub>2</sub> PERCENTAGE IN ALVEOLAR AIR DURING OBSERVATIONS
	Before	During	Before	During	
XXIV	1080	1845	0.82	1.63	14.4
XXVIII	600	1200	0.69	1.58	15.34
XXVI	905	2000	0.85	1.02	15.25
XXIX	1120	2250	0.85	1.27	17.7

*Changes in hydrogen ion concentration in the sweat and urine following exercise and heat.* GEORGE A. TALBERT.

Data were presented in support of the following conclusions:

1. That intense exercise of only twenty minutes duration will increase the acidity of the urine.
2. That heat produced in a sweat cabinet will in a large majority of cases increase the acidity of the urine of the subject.
3. That the sweat of man whether produced by exercise or heat is most invariably acid.
4. That heat sweat is always more acid than work sweat.

*The effect of shattered hemoprotein on the colorless blood corpuscles.* CLYDE BROOKS.

A protein substance has been isolated from the blood fibrin of the ox which though there is no toxic action produces an artificial leucocytosis. This substance is prepared by the methods previously outlined.<sup>1</sup> The main purpose has been to separate the protein from the blood without destroying the labile molecules which are apparently active in producing the leucotonic action. These labile molecules may be enzymes, vitamins or various adsorbed bodies which might cling to the fibrin as it is first coagulated.

When this protein is injected intravenously or intramuscularly it induces an artificial leucocytosis. There is no apparent preliminary sinking of the number of polymorphonuclear leucocytes immediately following the injection, but a steady upward trend. After several hours new or young leucocytes, and also atypical leucocytes appear in the blood stream, very much as after the injection of typhoid vaccine.<sup>2</sup> There is no reaction (chill followed by elevation of temperature, etc.) following the injection of the protein.

*On the relation between the velocity of Beta rays from radium and their physiological effect.* ALFRED C. REDFIELD.

The physiological effects upon the eggs of nereis of homogeneous groups of Beta rays of different velocities are proportional to their ability to ionize air. Beta rays of low velocity produce a greater amount of physiological change than the same number of rays of high velocity.

<sup>1</sup> Science, February 23, 1919; N. Y. Med. Journ., March 15, 1919.

<sup>2</sup> Cowie: Arch. Int. Med., 1919; Journ. Amer. Med. Assoc., April, 1919.

These conclusions are consistent with, but do not prove the view that the physiological effects of radiations from radium and x-rays are due to the production by them of an ionization of protoplasm.

*The concentration of alcohol in the tissues of hens after inhalation.* T. M. CARPENTER and E. B. BABCOCK.

Hens weighing about 2 kilos were placed in a 216 liter air-tight chamber saturated with alcohol vapor over periods varying from two to twenty-nine hours. The carbon dioxide was absorbed by partially slaked lime and oxygen was supplied from a well counterpoised spirometer connected to the chamber. The activity of the individual hens was registered by the method devised by Benedict. The animals were killed immediately after exposure and the alcohol distilled from the various tissues and determined by the Nicloux method. The amounts of alcohol per gram of the whole body and length of exposure are given in the following table:

*Alcohol in hens after inhalation of its vapor (Milligrams of alcohol per gram of whole body)*

HEN NUMBER	HOURS EXPOSED	ALCOHOL PER GRAM	HEN NUMBER	HOURS EXPOSED	ALCOHOL PER GRAM	HEN NUMBER	HOURS EXPOSED	ALCOHOL PER GRAM
42	16	0.03	10	27½	0.64	11	15½	2.19
37	2	0.06	29	16	0.81	13	15½	2.24
38	2	0.18	46	16	1.13	3	15½	2.26
39	2	0.20	33	8	1.38	44	16	2.35
25	3	0.25	24	8	1.51	35	4	2.43
21	4	0.27	40	16	1.68	9	29	2.51
5	16½	0.28	34	4	1.73	45	16½	2.77
43	16½	0.33	48	16	1.98	8	29	3.27
41	16	0.34	47	16	2.06	6	29	5.67
36	4	0.38	15	8	2.13			

Hens 5 and 10 were very active practically the entire time during their stay in the chamber.

Hens 40 to 48 were stimulated to activity intermittently with varying degrees of success by means of leads from an induction coil. All hens containing more than 1.5 mgm. of alcohol per gram of body substance showed signs of intoxication.

The relative concentration of alcohol of different tissues of 12 hens was on the average as follows:

Blood.....	100
Heart and lungs.....	86
Brain.....	84
Kidneys.....	79
Alimentary tract.....	78
Muscle.....	78
Spleen.....	75
Liver.....	72
Skin.....	56
Fat.....	11
Whole body.....	70

Three dead hens placed in the chamber for sixteen hours gave 1.15 to 1.22 and 2.09 mgm. of alcohol per gram. Diffusion through the skin played a rôle in the experiments with live hens as well as inhalation.

*The metabolism of bile acids.* M. G. FOSTER, C. W. HOOPER and G. H. WHIPPLE.

Very little work has been reported recently dealing with the bile salts, for the methods of analysis available are not only inexact but very laborious. Many substances present in bile are known to interfere seriously with the various published methods for bile acid determination. It is generally accepted that dog's bile contains only taurocholic and taurocholic acids with, at the most, only a trace of glycocholic acid. The presence of 10 per cent glycocholic acid in the bile acid fraction will not modify the figures computed as taurocholic acid by our method.

A new method has been devised which consists in simple hydrolysis of mucin-free bile with sodium hydrate at the temperature of boiling water. Taurocholic acid is completely split into taurine and cholic acid. The taurine is estimated by the Van Slyke amino nitrogen technique, as we have found that taurine gives up all of its amino nitrogen in three minutes. By this method taurocholic acid, added in known amounts to bile, can be quantitatively recovered. Other substances known to be present in bile do not interfere with this method, which has an error not exceeding 6 to 8 per cent.

All observations were made upon bile fistula dogs which were in a normal condition of activity, weight and appetite. These dogs were kept on a careful routine of diet, exercise and bile collection. Six-hour collections were made daily with a thirty-minute period of preliminary drainage of the bile fistula. Like many other workers, we observed great variations in the excretion of bile acids in these bile fistula animals, but we found it possible to reduce these fluctuations in large measure by *diet control*. During fasting periods, these dogs approach a uniform level of bile acid elimination, but even in such periods there are fluctuations which we cannot explain. The elimination from hour to hour during the day is fairly uniform for any given dog, but the daily output may vary a good deal. As a rule the bile acid excretion is a little higher in the forenoon than in the afternoon.

Diets rich in meat proteins raise the level of bile acid output to a maximum, and periods of fasting will depress the bile acid output, not to zero, but to about 25 to 35 per cent of this maximum. Sugar feeding will depress the bile acids below the fasting level of excretion. It is evident that there is an endogenous as well as an exogenous source of bile acids. After periods of fasting, a diet rich in meat proteins will not lift the bile acid output to the usual maximum level, and may raise it scarcely at all for several days. This may indicate a deviation of certain food elements from bile acid formation to tissue protein construction. This is only one of many suggestive points which seem to indicate an important relationship between the *body protein* metabolism and the *bile acid* metabolism.



Small amounts of bile given by mouth show a prompt excretion of the contained bile acids within three to four hours. If not over 2 grams of taurocholic acid are given by mouth, we may expect about 90 per cent elimination in the bile within four hours. Large amounts of bile acids given by mouth may prolong this elimination over many hours or even days and the cholagogue action may last even longer than the increased bile acid excretion. By giving sugar with bile acids by mouth, the cholagogue action can be inhibited and a maximum concentration of bile acids in bile (7 to 9 per cent) may be attained in this way. Bile given at night in moderate amounts has no influence upon the bile acid output of the following day. Bile exclusion by means of a night abdominal binder to prevent any licking of the fistula does not modify the curve of bile acid elimination in our experiments. This holds for all diet experiments as well as for periods of fasting.

Taurine intravenously or by mouth does not influence bile acid elimination. Taurine plus cholic acid by mouth reacts exactly as does taurocholic acid and causes a cholagogue action with great increase in output of bile acids. Cholic acid alone gives a cholagogue action and with a rich nitrogen diet causes a great rise in bile acid output. This is not true during fasting periods and we must assume that this increase in bile acid production is limited by the amount of available taurine either from food or tissue protein. Cystine injection alone does not influence bile acid excretion but combined with cholic acid feeding reacts exactly as does taurine. This confirms other work to show that taurine is derived from the amino acid cystine.

Cholic acid is of unknown origin in the body. It gives certain chemical reactions like cholesterol, turpentine and camphor. Cholesterol feeding and the feeding of large amounts of red blood cells did not influence the output of bile acids in bile. Intravenous injection of large amounts of laked red blood cells was also negative. Feeding terpene hydrate and camphor alone or combined with taurine gave no positive results. Casein, caseinamino acids, beef extract (commercial) and gelatin feeding have no influence upon the bile acid excretion. Our experiments seem to indicate the derivation of cholic acid either from certain meat proteins in the food, or from the tissue proteins, or both. Cholic acid is normally the limiting factor which determines the level of bile acid excretion in bile fistula dogs.

*On the compensation of ocular and equilibrium disturbances which follow unilateral removal of the otic labyrinth. Demonstration.*<sup>1</sup> ALEXANDER L. PRINCE.

The ocular and equilibrium disturbances which follow unilateral destruction of the otic labyrinth in higher vertebrates are of short duration and are ascribed to the unbalanced activity of the intact labyrinth.<sup>2</sup> In the cat, these disturbances consist of deviation of the

<sup>1</sup> A report of these experiments appeared in the Proc. for Exper. Biol. and Med., 1917, xiv, 133.

<sup>2</sup> Wilson and Pike: Phil. Trans. Royal Soc., London, 1912, Series B, cciii, 127.



eyes toward the side of the lesion, accompanied by nystagmus, and of a tendency to roll, fall and execute circus movements, also in the direction of the injured side. These symptoms gradually diminish in intensity and have disappeared within forty-eight to seventy-two hours after operation.

The question arises as to the mechanism concerned in the disappearance of the disturbances occasioned by the removal of the labyrinth.

In the animals demonstrated, decerebration was performed, several weeks after complete recovery from the effects of the labyrinthine operation, by section of the brain stem just anterior to the corpora quadrigemina. This procedure is immediately followed by deviation of the eyes to the side of the lesion and recurrence of the symptoms of disturbed equilibration.

In view of these observations, the disappearance of the ocular and equilibrium disturbances following unilateral removal of the labyrinth is attributed to the activity of a compensatory mechanism. The nervous paths concerned in the process of compensation may be roughly localized in the cerebrum above the level of the corpora quadrigemina.

*A new type of rebreather. Demonstration.* CARL N. LARSON.

To obviate the immobility of the Henderson-Pierce rebreather the capacity of which is controlled by intake and outlet of water (requiring water and sewer connections) a new type of rebreather has been devised and installed in the Medical Research Laboratory of the Air Service, War Department. The new form is light and portable, it is free from water system connections, it can be graduated so that the oxygen percentage of the inclosed air is known at every moment and checking gas analyses can be made at any moment during the progress of a test. The rate and volume of the respirations and of the oxygen consumption can be taken directly by the automatic recorder devised by the author and from the table of constants of the instrument.

A brief description of the new features of the machine is as follows: The air chamber is of two pieces suitably framed and supported. The lower piece is a double cylinder with common base and open at the top. Each is 15 inches high and the inner cylinder 14 inches in diameter. A space of 1 inch filled with water serves as a water seal. The upper part of the cylinder is single, open at the bottom to engage with the lower cylinder in the water seal. It is 15 inches tall by 15 inches in diameter. The movable lower portion is raised into position by its crank shaft and ratchet. The capacity of the instrument can be varied between 40 and 80 liters. In the center of the top section a water sealed spirometer of 6 liters capacity is countersunk. It opens directly and widely into the air chamber insuring even mixture of the contained air during the re-breathing. The top of the tank carries openings for inspiratory and expiratory tubes controlled as in the Henderson-Pierce rebreather type. Two tubes controlled by valves open directly into the air chamber, one for introducing nitrogen, oxygen or other gases and the other for withdrawing samples for analysis. The whole apparatus by modify-

ing the size lends itself for use in respiration experiments of either physiological or pharmacological import on man or mammals.

*The work of the United States Public Health Service in industrial physiology.* FREDERIC S. LEE.

Since June, 1917, the Public Health Service has been carrying on an investigation of some of the problems of industrial physiology. The work is still continuing. Two representative factories have been studied, an eight-hour factory employing 36,000 workers with three shifts, and a ten-hour factory employing a maximum of 13,000 workers with two shifts. The subjects studied include the following: Diurnal course of output; lost time; stereotyped output; day versus night work; rest periods; accidents; labor turnover; muscular strength of workers; fatigue of workers; rhythm in industrial operation; some of the chemical phenomena of fatigue. The results will be presented in detail in a general report, which is soon to appear, and in special reports dealing with particular topics. Some of the broader features of the results are as follows:

1. *Maintenance of output.* In the eight-hour plant there is a more steady maintenance of production throughout the day; in the ten-hour plant, there is a marked decline of production at the end of each shift.

2. *Lost time.* In the eight-hour plant, work with almost full power begins and ends approximately on schedule and lost time is reduced to a minimum; in the ten-hour plant, work ceases before the end of the spell and lost time is abundant.

3. *Stereotyped output.* By this is meant the voluntary restriction of production by the worker. In the eight-hour plant, a stereotyped output is comparatively rare and production approximates physiological capacity; in the ten-hour plant, stereotyped output is very prevalent.

4. *Night work.* In the ten-hour plant, a twelve-hour night shift prevails. The output is characterized by a progressive decrease and an abrupt and marked fall during the last two hours. This suggests the advisability of shortening the duration of the night work in the interest of greater production.

5. *Rest periods.* Rest periods of ten minutes' duration during each of the two working spells were introduced in several departments of the two factories. In the eight-hour plant, the result was indeterminate; in the ten-hour plant, while there was great individual variation among the workers, in eleven of the twelve operations studied, the total output of the day was increased.

*Rhythm in industry.* A. H. RYAN and P. S. FLORENCE.<sup>1</sup>

Rhythmical movements, such as those occurring in machine operations, are characterized externally by an approximately uniform repetition. The time interval between operations or various steps in operations can be measured, and such measurements may be used as an index

<sup>1</sup> From the U. S. Public Health Service.

of the rhythm. A method was devised of fitting up the machine to be studied with electrical contacts so that each step in the operation could be recorded automatically. Chronometer records were obtained simultaneously, and by means of a signal magnet records were also made of any variations in the work or working conditions.

We have chosen the median speed of a series of operations as that more nearly representing the typical speed. From this the average deviation was obtained, and this divided by the median gives the percentage deviation from the median, or the coefficient of dispersion. The smaller this coefficient, the more rhythmical the operation or operator.

In a simple movement, such as tapping, the coefficient of dispersion on two subjects was 2.40 per cent and 2.54 per cent. In the facing and scoring fuse ring (handscrew-machine type) the coefficient in one operator was as low as 2.74 per cent. In the inexperienced worker the coefficient was as high as 8.34 per cent. In five operators on this machine the more experienced and faster operators gave the lowest coefficients. In 45 series of observations on the same worker, covering 2648 operations, the coefficient was 4.22 per cent. In beveling (also a handscrew-machine operation) the coefficient was likewise low. In the foot-press type of operation the coefficient was considerably higher, indicating less rhythm.

The fatigue of the day did not seem to lessen the rhythm of the operation. Distraction, such as counting the ringing of a bell, did not seem to interfere with the rhythm. A curve expressing the correlation of speed and rhythm indicates that there is an optimum speed for rhythm and that the rhythm is worse at either a slower or faster speed.

The possible importance of rhythm in industry and occupational fatigue may be briefly summarized as follows:

1. In relieving attention and its consequent fatigue.
2. In rendering more uniform the metabolism and recovery involved in the operation by evenly distributing the work.
3. In masking fatigue effects. Here the output curve may be maintained in spite of fatigue.
4. In increasing or decreasing accident hazard according to the type of accident causation.

*Muscular tonus in relation to fatigue.* A. H. RYAN and SARA JORDAN, with the collaboration of A. B. YATES.<sup>1</sup>

Tonus was investigated in the hope of finding further methods for the detection of the more pronounced degrees of fatigue resulting from the day's work at different occupations and from the working day of different lengths, also for cumulative fatigue. This is a preliminary report of the results.

Among the methods devised by us was that of determining at different times the amount of tension required to produce a given amount of extension of a group of muscles. Present results are based on observa-

<sup>1</sup> From the U. S. Public Health Service.

tions made upon the pectorales and the soleus-gastrocnemius group. For the pectoral measurement the subject was placed in a standing position in an apparatus with his back resting against a support; the arms were elevated to the horizontal position and supported in metal slings suspended from the ceiling. One arm was fixed to an immovable standard while the other was pulled backward a constant distance by means of a cord and pulley. A delicate spring balance was inserted between the cord and the arm sling. A rigid graduated arc below the arm made it possible to achieve a constant extension at the different observations. In testing the soleus-gastrocnemius group the subject either sat or reclined on a table. The apparatus consisted of an upright board hinged to a horizontal board which was clamped to the table. The foot was fastened to the upright board and the axis of rotation about the hinge passed through the ankle. A handle with spring and scale attached made it possible to apply pressure in such a manner that the soleus-gastrocnemius group was extended, and to observe the degree of extension and pressure. The amount of tension required to produce a given degree of extension at the various times of observation was taken as the index of muscle tonus. A history was kept of sleep, work, rest, etc.

In subjects doing relatively strenuous work during the day, or where long hours were being spent in work, there was usually a decrease in the tonus in the evening as compared with the morning condition. This was more pronounced when the subject was losing rest (sleep). After lost rest the morning tonus was lower and the average tonus for the day was less than on days following a good night's sleep. Evidence was thus obtained of cumulative fatigue effects. Sleep at night or during the day was usually followed by a considerable increase in tonus. Strenuous work of short duration was usually followed by an immediate decrease in tonus. Psychic influences (excitement) seemed occasionally to produce an increase in tonus, although fatigue-producing conditions were recorded in the history. In subjects doing relatively light work and obtaining plenty of sleep the tonus varied during the day, the evening tonus being frequently greater than that observed in the morning.

*The effect of fatigue on the bicarbonate content of blood plasma.* A. BAIRD  
HASTINGS.

The following is a preliminary report of studies on fatigue conducted in the laboratory and in the field as a part of the program of the United States Public Health Service.

Evidence of the production and accumulation of fatigue substances in the organism was sought by studying the bicarbonate content of the blood plasma of normal animals. The Van Slyke apparatus for the determination of carbon dioxide and the McClendon electrode for the electrometric titration of plasma were employed to measure the bicarbonate content. The Clark hydrogen electrode was used to determine the reaction of the plasma. Fatigue was induced by causing the animals to run on a motor-driven treadmill whose speed could be varied up to ten miles per hour.

Fifty-five experiments on fifteen dogs, several rabbits and one man have yielded results of which the following example is typical. The bicarbonate content of the plasma of dog A, running continuously at an average speed of 6.7 miles per hour for 43.7 miles dropped from 57.5 to 47.9 volumes per cent of  $\text{CO}_2$ . The corresponding  $\text{P}_H$  values were 7.72 and 7.71. No significant differences of hydrogen ion concentration were found in plasma collected before and after fatigue even though the bicarbonate content had fallen 31 per cent. The rate and the maximum amount of fall of the plasma bicarbonate during the same degree of exercise varied from subject to subject. It may be stated, however, that in any one organism the rate of diminution of the bicarbonate content, was, within certain limits, a function of the rate of fatigue. Further, when the rate of exercise was below that required to exact from the subject his maximum muscular performance, the fall in the bicarbonate seemed to vary almost directly with the distance traveled. The bicarbonate of small dogs whose capacity for muscular activity could be quickly reached by the available speed of the treadmill, fell rapidly to a constant level, thereafter necessitating a gradual reduction in speed to permit them to keep in motion. With regard to the rate at which the reserve alkali returned to its normal concentration, it was found that in an animal which had been fatigued by running at a rapid rate for a comparatively short distance, the recovery was rapid; but when he had run a relatively long distance, the recovery was much slower. This would point to an accumulation of fatigue substances in the organism.

Results of  $\text{P}_H$  determinations of the urine of men exhibited no significant changes of the average hydrogen ion concentration in resting men, a slight increase in factory workers, and large increases in the case of men engaged in such strenuous exercise as participating in a Marathon or six-day bicycle race.

*Effects of external temperature upon the toxicity of thyroid.* O. O. STOLAND and MAY KINNEY.

The toxic dose of desiccated thyroid reported by different investigators varies greatly and since no satisfactory explanation for such variation has been offered, we have attempted to find the cause for such variation.

Three series of albino rats, fed on a diet consisting of crackers and milk, were kept at different temperatures, 32, 25 and 18°C. All except a few controls in each series were fed 0.2 gram of desiccated thyroid per day. The series kept at 32° lived an average of 7.3 days; that at 25°, twenty-two days and that at 18° more than thirty-two days. The toxicity, therefore, varies with the temperature, being greater with the higher temperatures.

The histological changes of the thyroid observed were as follows: All the animals fed on 0.2 gram thyroid per day developed the normal resting type of gland with low cuboidal epithelium. The controls kept at 32 and 25°C. also showed the resting type of gland, but the controls kept at 18°C. developed the active type of gland with small amount of colloid and columnar epithelium.



We would conclude: *a*, that external temperature is an important factor in determining the toxicity of thyroid gland fed to susceptible animals; and *b*, that in conditions which produce hyperplasia of the gland, hyperthyroidism produced by feeding of desiccated thyroid will bring about a change to the resting type of gland.

*Physiological action of the thyroid hormone.* E. C. KENDALL.

Thyroxin when injected into the animal organism does not produce any immediate physiological effect and if but a single administration is given a demonstrable action may not be produced. This applies to relatively enormous doses of the substance and it shows that the compound itself is not toxic. The toxic condition which is noted in thyroid disturbances and which can be readily produced by thyroxin results only after a long-continued administration of the substance. Three or four successive daily administrations are necessary in order to bring about a hyper-thyroidism. Investigation showed that thyroxin is rapidly eliminated from the body by means of the bile. In one case, over 60 per cent was thus excreted. Eight per cent of the iodine in the administered thyroxin was found in the urine and the remaining 32 per cent had doubtless been taken up by the thyroid of the animal. This explains why the single administration does not produce a physiological response. It is only the continued presence of the compound within the body which results in the increase in metabolic activity.

A method for the determination of minute amounts of iodine has been devised and it has been found that the average content in calves' blood is approximately 0.015 mgm. per 100 cc. of blood. The amount in the tissues is slightly greater, about 0.03 mgm. per 100 grams of tissue. The amount in the liver is still slightly greater, about 0.04 mgm. per 100 grams of liver. These figures show the very small amount of thyroxin functioning within the tissues, but they agree very well with the amount that must be there in order to satisfy the quantitative relation which thyroxin bears to basal metabolic rate. This relation has been found to be: 1 mgm. of thyroxin increases the basal metabolic rate 2 per cent in an adult weighing approximately 150 pounds.

The administration of thyroxin to the animal organism has been shown to produce an effect upon the metabolic rate which bears a quantitative relation to the amount administered. An injection of a derivative of thyroxin in which the hydrogen of the imino group is replaced has no effect upon the metabolic rate. This emphasizes the importance of the imino group in thyroxin and minimizes the importance of the iodine in the molecule. Other investigators have recently shown that in the metamorphosis of the tadpole the administration of iodine produced a great increase in the rate of metamorphosis. If the metamorphosis depends only upon the increase in the basal metabolic rate of the tadpole then thyroxin should increase the rate of the metamorphosis, but the derivative involving the imino group should not. If, however, iodine alone were concerned in accelerating the metamorphosis, then both thyroxin and the derivative should affect the metamorphosis. It was



found that both thyroxin and the derivative would cause a rapid metamorphosis of the tadpole of the bullfrog.

Thyroxin, therefore, appears to have two separate and distinct functions: The effect upon the metabolic rate which is brought about by the CO-NH groups within the molecule; and the physiological changes involved in the metamorphosis of the tadpole brought about by the iodine contained in the molecule. This action of the iodine is not specific to thyroxin, but can be obtained by a large number of other iodine compounds and by elemental iodine itself and appears to be inherent within the iodine atom. But the unique effect of thyroxin on the metabolic rate is due to the specific chemical structure of the molecule and this is not shared with any other substance so far known.

*The pharmacology of acacia.* THEO. K. KRUSE.

1. A 25 per cent solution of acacia causes hemolysis, agglutination and darkening of blood. Such a solution is about one-third isotonic with blood. If such a solution is made up in saline, hemolysis is largely prevented.

2. Agglutination occurs in man, dog, cat and rabbit and does not occur in ox, frog and turtle. This phenomenon is not associated with viscosity, acidity, alkalinity nor the calcium content of acacia. Hypertonic solutions delay but do not prevent agglutination.

3. Rhythmicity of isolated tissues such as smooth muscle and cardiac strips is diminished, even in concentration of 0.01 to 0.1 per cent acacia in saline.

4. Urine secretion is decreased and sometimes nearly suppressed after acacia injection. This is a factor in the maintenance of blood volume by acacia.

5. Blood volume is well maintained partly at the expense of urine excretion.

6. Gum acacia does not mix readily with blood.

7. Acacia is tolerated in normal animals. In animals reduced by hemorrhage acacia is not tolerated, showing irregularities of heart and no improvement in blood pressure until blood, saline, dextrose or sucrose are subsequently injected. A 6 per cent acacia in 2 per cent sodium bicarbonate is less toxic. This is probably brought about by its increase in osmotic tension and by the augmenting effect of sodium bicarbonate upon the heart.

8. Pharmacological evidence does not support the use of acacia in man.

*The treatment of the condition of low blood pressure which follows the exposure of the abdominal viscera.* F. C. MANN.

The purpose of the investigation is to review experimentally all the more important methods of treating a condition which exhibits the clinical signs of surgical shock. The method of experimentation consists in exposing the abdominal viscera of a dog under a constant ether tension until blood pressure is decreased to the desired level, therapeutic procedures are then instituted.

The methods of treatment are divided into four divisions: (1) general measures; (2) special measures; (3) the use of drugs; and (4) attempts to restore fluid volume. The last method was investigated very extensively. It was found that under the experimental conditions blood or blood serum produced by far the best results. None of the artificial solutions were as beneficial as blood. Of the artificial solutions, normal salt solution was the least valuable and did not seem to produce as good results as distilled water. A hypertonic salt solution produced better results than a normal physiologic solution. Sodium carbonate and sodium bicarbonate produced some beneficial action as did also sodium sulphate. None of the saline solutions alone would restore and maintain blood pressure. Glucose was found to be of distinct benefit as were also cane sugar solutions. The so-called colloidal solutions produced the best results of all the artificial media. Gelatin solutions were found to be fully as efficacious as acacia solutions. Neither of these solutions appears to be without danger. Solutions of dextrin produced fair results. Various combinations of these different solutions were tried but none of them were found to be of as great value as blood.

*The nutritive value of yeast protein.* THOMAS B. OSBORNE and LAFAYETTE B. MENDEL.

A graphic record was presented of the growth of rats beginning at ages of thirty-five to forty-five days for a year or more on a diet in which the protein and water-soluble vitamins were furnished by brewers' yeast alone. The foods consisted of:

	per cent
Yeast.....	30-40
Salt mixture.....	4
Starch.....	43-53
Butter fat.....	9
Lard.....	14

It is evident that the protein of yeast is "adequate" in the ordinary sense for nutrition. Details of this study will be published in the *Journal of Biological Chemistry*.

*Further studies on the chemical composition of the brain of normal and ataxic (?) pigeons.* MATHILDE L. KOCH and OSCAR RIDDLE.

Previous observations of functional derangement in pigeons, i.e., lack of control of the voluntary movements—provisionally called ataxia—led to the conclusion that the seat of the disturbance was probably in the brain. Previous chemical analysis of the brain of these ataxic pigeons supplied evidence that the functional disorder is associated with deviations from the normal composition of the brain. These were interpreted as indicating chemical under-differentiation or immaturity of the brain of the affected individual. In other words, the brains of affected individuals of a given age appeared chemically more like the brains of normal individuals of a younger age. To confirm this, ten additional analyses were made of brains of pigeons of still other ages than those previously used, in order to obtain more complete data on the chemical

changes of the brain during development. Also, in order to determine whether this functional disorder was localized, most of the analyses were upon samples representing separate portions of the brain—the cerebrum having been analyzed apart from the rest of the brain (cerebellum and medulla).

The principal chemical changes noted in the growth series (from 45 to 2021 days) are: a general decrease in the per cent of water (82.6 to 78.4 per cent), of proteins (51.9 to 47.4 per cent) and of extractives (14.4 to 13.2 per cent) and an increase of lipoids (33.7 to 39.4 per cent). The younger affected pigeon brains suggested greater chemical under-differentiation or immaturity than older affected brains. There appeared no or slight localization of changes in composition in the two parts of the brain analyzed, i.e., changes are a little more pronounced in the cerebellum. That the brain is the seat of the disturbance in these ataxic pigeons has been partially confirmed by chemical analysis, the younger "most ataxic" pigeons showing the greater chemical under-differentiation.

*Effect of pulse rate on the length of the systoles and diastoles of the normal human heart in the standing position.* WARREN P. LOMBARD and OTIS M. COPE.

Continuing the work reported at the last meeting, the writers have now material consisting of 620 tests on 250 men and 15 women, and have estimated, in thousandths of a second, the length of the systoles and diastoles of more than 10,000 heart cycles. The carotid pulse and the respiration were recorded by tambours, and the time was written by a fork having fifty v. d. The records were taken on loops of smoked paper 170 cm. long. All readings were made under a glass, verticals being drawn from the point where the primary rise of the pulse first turned sharply up, and from the point where the bottom of the dirotic notch was first reached. At least 15 consecutive cycles of each test were read. Diastoles are always affected by respiratory and usually by vasomotor influences; either one may show the more prominently in the plotted curves. Systoles always show the effects of respirations and sometimes vasomotor influences can be detected. As diastoles are longer and more variable than systoles, they have greater effect in determining the length of the pulse. The pulse rate, estimated from the length of individual cycles, may change 20 beats in a minute. If curves of the length of successive systoles and diastoles be plotted one above the other, and the time of the respirations is also indicated, the diastoles are seen to shorten promptly in inspiration and lengthen promptly in expiration. The systoles may or may not do this. The change in systole length may be delayed (just like the change in arterial blood pressure) so that the systoles may lengthen in inspiration.

If the average lengths of the systoles and diastoles of 250 men in the standing position are compared with their average pulse rates, and are plotted in a chart, in which the ordinates give the length of the systoles and diastoles in thousandths of a second and the abscissae the pulse

rates from 50 to 110, one sees that both the systoles and diastoles shorten as the pulse quickens, and that the diastoles shorten so much more rapidly than the systoles that the curves would have crossed had they been continued.

Accepting this chart as a standard, we found that the systoles of 84.8 per cent of the men differed not more than 0.015 second from the standard, 94 per cent not more than 0.020 second, and 6 per cent varied 0.021 to 0.025 second. The results obtained from the same man in two tests made perhaps weeks apart, generally agree better than might be expected, considering the probable difference in circulatory conditions. We found in the case of 68 men who were examined twice, 69.5 per cent gave systoles either longer or shorter than the standard each time. Also that in 75 per cent, the length of the systoles differed in the two tests less than 0.010 second.

One interesting fact observed was that of 15 women all gave systoles longer than the average length of systoles of men at the corresponding pulse rates in the standing position.

*Effect of posture on the length of the systole of the human heart.* WARREN P. LOMPARD and OTIS M. COPE.

The frequency of the beats of the left ventricle and, consequently, the pulse rate is determined by the rate of discharge of excitations from the sino-auricular node. One excitation starts the systole and the next excitation brings the diastole to an end. It is not known what influence stops the systole and starts the diastole. As the pulse rate quickens the length of systole lessens slowly and the diastole very rapidly. The shorter systoles might be associated with the lessened amount of venous blood reaching the heart during the short diastoles. Is there evidence that the amount of blood supplied to the large veins influences the length of the systoles of the left ventricle? Posture of body, by effects of gravity, would alter the rate of the return of blood to the large veins, and we have found that by the same heart rate the systoles of the left ventricle are 10 per cent longer in the sitting position, and 14 per cent longer in the lying-down position, than in the standing posture. This can be readily seen in a chart in which the average length of the systoles is plotted with respect to the average pulse rates by standing, sitting and lying-down postures. The change in the length of the systoles by different positions is not due to the changes in the rate of the pulse alone, because the systoles change out of proportion to the pulse. The curve of the average length of systoles has been found to correspond to the

curve given by the formula  $S = \frac{60}{K \sqrt{R}}$ , in which  $S$  = systole,  $K$  = a constant and  $R$  = pulse rate. For standing postures a suitable constant appears to be 28.5, for sitting 26 and for lying down 25. It has also been found that the systole length in the standing posture just after exercise is slightly longer than before exercise, and the constant has to be changed from 28.5 to 27.5. Probably blood is returning to the heart more rapidly just after exercise. Height, and time of year,

have not been found to affect the length of systole. The effects of age of muscular exercise and of arterial blood pressure are being studied. As was stated in our first paper, the length of the systoles of the 15 women studied was longer than the average of men with corresponding pulse rates in the standing position. All but one of the women had longer systoles than men in all positions. Four women gave systoles not more than 0.008 second longer than men in the standing position. Three of these women reported having had considerable physical training, and two of the three gave systoles shorter than the average length given by men in the standing position just after exercise. One, who had 5 years gymnasium experience, gave systoles longer than men not only after exercise but in the sitting and lying-down positions. One cannot help wondering whether the longer systoles shown by women are due to the fact that most women take little vigorous exercise.

*A comparative study of the relation of the cerebral cortex to labyrinthine nystagmus.* A. C. IVY.

During a series of cerebral ablations, it was suggested by Dr. F. T. Rogers that observations be made upon the nystagmus reaction. Wilson and Pike<sup>1</sup> and later Pike<sup>2</sup> have reported that the quick component of nystagmus was dependent upon the integrity of a cerebral reflex arc, i.e., the "removal of one cerebral hemisphere abolishes the quick movement when the slow movement of the eyes is directed to that side," or the removal of "the temporal and basal portion of the cerebral hemisphere" on both sides would completely abolish the quick component of nystagmus. Bauer and Leidler<sup>3</sup> report that the quick component is not dependent upon the cerebral cortex and thalamus and that with even extensive destruction of the mid-brain and probably with inclusion of the third nucleus does not abolish vestibular nystagmus.

This work has been done upon frogs, turtles, pigeons, rabbits, kittens, cats, pups and dogs. All operations upon mammals were done aseptically. When animals were comatose and when pressure symptoms were manifest, notation of such was made. Many of the animals lived indefinitely, or until some more radical operation was done. Observations have been made only upon rotatory and post-rotatory nystagmus, the speed and number of rotations being carefully controlled.

The brains of all operated animals have been examined and preserved. A quick movement of the eyes upon rotation is present in the frog. It is irregular and slight in degree, for the deviation of the eye in the frog on rotation is not marked. It is influenced by such factors as temperature, handling and amount of rotation. Decerebration does not abolish the quick movement, but often increases the reaction.

A true eye, as well as head and neck, nystagmus is present in the turtle provided the temperature of the turtle is between 10°C. and 39°C. Following decerebration there follows a marked increase in the post-rotatory

<sup>1</sup> Wilson and Pike: Arch. Int. Med., 1915, xv, 31.

<sup>2</sup> Pike: Proc. Soc. Exper. Biol. and Med., 1917, xiv, 76.

<sup>3</sup> Bauer and Leidler: Monatsch. f. Ohrenheilkunde, 1911, xlv.



tory response. Destruction of the cortex of the optic lobe does not abolish the quick component, but injury to the basal portion of the optic lobe does.

Complete decerebration with extensive injury of the thalamus in the pigeon does not abolish the quick component provided the temperature of the bird is kept normal by keeping the bird in an incubator. Rogers<sup>1</sup> has shown that in such animals all reflexes are diminished, or disappear, if the temperature of the bird is not normal.

In dogs hemi-decerebration and extensive injury to the thalamus does not abolish the quick component of nystagmus, but causes a temporary (3 to 4 months) increase in the post-rotatory nystagmus when the animal is rotated opposite to the side of the lesion. The rotatory nystagmus is increased when rotation is to the side of the lesion. The increase consists chiefly in a greater number of movements rather than an increase in the period of duration, which, however, does occur. If the remaining motor area is removed in a hemi-decerebrate animal, an increase in the post-rotatory nystagmus occurs when the animal is rotated opposite to the side of the fresh lesion. If the animal is comatose, manifests marked pressure symptoms, or if there is an injury to the third nerve, the quick component of nystagmus is absent, although deviation is present.

Rabbits and cats manifest the same results. Kittens and pups likewise show the same phenomena but the increase is more temporary, i.e., does not last longer than from four to six weeks.

Hence the conclusion is warranted that the quick component of eye nystagmus is not due to the integrity of a cerebral reflex arc, but is a lower type of reflex over which the cerebrum exercises its well recognized inhibitory influence. It is not meant by this that the cerebrum has the power to voluntarily reduce the number of nystagmic reactions following rotation.

*Studies on the secretion of the pyloric end of the stomach.* A. C. IVY.

Heidenhain<sup>2</sup> demonstrated that the pyloric mucous membrane produced a thick, clear, alkaline secretion, which digested fibrin and coagulated milk.

In a series of animals prepared like Heidenhain's dog and in another series prepared with pyloric pouch with nerves intact, observations upon the character of the pyloric secretion have been made.

The rate of secretion of the entire pyloric mucous membrane is 2 cc. (average) per hour in animals with an isolated pouch. In animals with nerve supply to the pouch intact the rate of secretion is 5 cc. (average). The secretion is more or less continuous, no significant increase occurring after meals or water. The secretion is not increased in amount by subcutaneous injections of either gastrin or secretin. It shows no variations in amount with changes in the character of the food.

<sup>1</sup> Rogers: Journ. Nervous and Mental Diseases, 1919, xlix, no. 1.

<sup>2</sup> Heidenhain: Arch. f. d. gesamt. Physiol., 1878, xviii.



The secretion is thick and viscid—very similar to egg white. It is clear and very slightly alkaline in reaction.

The pepsin content of the secretion from the isolated pouch is lower than that from the pouch with the nerves intact, the former amounting to 0.5 to 1 mm. (Schiff's modification of Mett's method), the latter amounting to 2 to 3 mm. No significant change occurs following a meal. There is a slight rise in peptic activity during the third and fourth hours after a meal. Subcutaneous injection of gastrin caused a slight increase in peptic activity.

Its specific gravity varies from 1.009 to 1.013.

Chemical analyses made by Mr. B. Raymond have given up to date the following results per 100 cc. of pyloric secretion: Total solids, from 1.331 grams to 1.795 grams; total ash, from 0.558 to 0.903 gram; total nitrogen, from 0.095 to 0.144 gram; total chlorides, from 0.458 to 0.519 gram.

*Studies on experimental gastric and duodenal ulcer.* A. C. IVY.

A study has been made *a*, of the occurrence of ulcer and other pathological lesions in the stomach and the duodenum of the dog; *b*, of the experimental production of chronic gastric ulcer in the dog; *c*, of the relation of the location of the ulcer to changes in gastric motility; *d*, and of the nervous mechanism involved in hypermotility of the stomach in experimental duodenal ulcer.

As judged from the results of eight hundred and fifty autopsies upon the stomach and duodenum in healthy and diseased dogs, it is apparent that chronic ulcer of the stomach and duodenum is very rare. In healthy dogs a chronic ulcer has never been found. In diseased experimental animals two typically chronic ulcers have been found, one in a thyroid-parathyroidectomized animal complicated by distemper, which was present prior to the operation, and a second in a ligated-pancreatic-duct animal, which was complicated by an acute stomatitis and cachexia. On the other hand petechial hemorrhages and hemorrhagic erosions are found not infrequently in the gastric and duodenal mucosa of the healthy dog. These lesions, however, occur much more frequently in the experimental and diseased and cachectic animals.

Typical chronic ulcers have been produced experimentally by making lesions of the pyloric and duodenal mucous membrane and then feeding cultures of virulent streptococci. A series of five healthy animals gave negative results, the lacerations of the mucous membrane healing in from six to ten days. A series of five cachectic animals showed indurated ulcers when they died or were killed four to six weeks following the lesion of the gastric mucous membrane. As a control, lacerations were made in two cachectic animals which were not fed streptococci. These lacerations healed in from twelve to fifteen days. The interpretation given to these results as related to the etiology of chronic gastric ulcer is as follows: given a petechial hemorrhage or an hemorrhagic erosion, along with a general lowered resistance accompanied by a hypo-acidity, bacteria swallowed are implanted in the abrasion, cause an inflammation

which is followed by an induration, which results in poor blood supply to the edges of the ulcerated area and an indefinite delay in the growth of mucous membrane to cover the abrasion. This work is being continued by a method more subject to experimental control.

In studying motility in ulcer, ulcers were made by the submucosal injection of 2 cc. of a 5 per cent silver nitrate solution. An ulcer located in the fundic portion of the stomach has no effect upon the motility and emptying time of the stomach. Ulcer in the pyloric portion of the stomach caused in three out of five dogs an increase in the motility of the empty stomach. In one of the five the emptying of the stomach was delayed two hours. Autopsy revealed an extensive scar just proximal to the pyloric sphincter. Ulcer of the duodenum caused an increase in the motility of the empty stomach in all of the six dogs studied. The emptying of the stomach was delayed more than two hours in every case. These results show that the clinical symptoms of ulcer with reference to disturbed motility and emptying time of the stomach and even loss of weight can practically be duplicated experimentally.

Animals with both vagi and both splanchnics cut along with excision of the coeliac plexus in which duodenal ulcers were made show an increase in motility of the empty stomach and a delayed emptying time.

In other words the mechanism of increased motility and delayed emptying of the stomach in duodenal ulcer is intrinsic. Whether it is due to increased irritability of the intrinsic nervous reflex or altered metabolic rate is yet to be determined.

*An experimental study of a possible mechanism for the excitation of infections of the pharynx and tonsils.*<sup>1</sup> STUART MUDD and SAMUEL B. GRANT.

The present experiments were undertaken in the hope of throwing light upon the mechanism by which chilling of the body surface may excite infection of the mucous membranes by their indigenous bacteria. The authors devised simple wire "applicators" for holding in apposition with the skin or exposed mucous surfaces the terminals of thermopiles in circuit with a D'Arsonval galvanometer. From the thermometer and galvanometer readings the temperatures of the surfaces beneath the thermopiles may be computed and temperature changes accurately followed.

The cutaneous chilling in our experiments caused only inconsequential changes in blood temperature and pressure. Rate and depth of respiration were kept constant. Superficial temperature varied directly with rate of blood supply, and was an index of local vasomotor tone. This thermogalvanometric method, checked by observations of color change, showed that chilling of the body surface causes reflex vasoconstriction and ischemia—not, as hitherto assumed, congestion—in the mucous membranes of the palate, faucial tonsils, oropharynx and nasopharynx.

Inhalation of amyl nitrite causes a sharp rise in mucous membrane

<sup>1</sup> The detailed paper will appear in the Journ. Med. Research, xl, no. 1.

temperature parallel to the skin flush. The temperature of an oropharynx, chronically inflamed for almost two years, failed to fall with cutaneous chilling, but normal vasodilatation followed amyl nitrite inhalation. The reflex arc to the mucous membrane vessels had thus presumably been interrupted in its peripheral motor elements. A throat with history of inflammation extending back only a week showed no blanching with chilling.

Scar tissue showed reflex vasoconstriction parallel to that of the neighboring skin. The earliest scar tested and proved to have vasomotor fibers was at the site of an operation performed a month before for removal of a keloid.

In four instances exposure was followed by a "cold" or sore throat.

It does not seem improbable that the ischemia of the mucous membranes incident upon cutaneous chilling might so disturb the equilibrium between the host and the bacteria in the tonsillar crypts and folds of the pharyngeal mucosa as to excite infection.

*The antiscorbutic properties of green malt.* J. F. McCLENDON and WYMAN C. C. COLE.

Owing to the scarcity of antiscorbutics in winter an investigation of their production indoors seemed worth while. Sprouted seeds and their extracts were shown by our collaborator, Paul F. Sharp, to have a greater hydrogen ion concentration than pure water and hence might be subjected to a certain amount of heat or storage in the moist state without entire loss of antiscorbutic properties. Cereal grains and legumes were chiefly used but the former were found to be more resistant to mould. Sprouted wheat, heated to 70°, is quite tender and palatable, and the same may be said of rye. Corn moulds easily but is sometimes utilizable. Barley has an adherent husk that makes it unsuitable for similar use but more suitable for malt extracts. A special mill for grinding green malt was devised. If the mash is brought momentarily to 70° the oxidases are partially destroyed and the wort may be evaporated in vacuo to a syrup that needs no sterilization or preservative. Since the wort is acid and never boiled and the malt is not dried the antiscorbutic properties are largely retained. Thirty-five guinea pigs have been used in testing the antiscorbutic properties of green malt and extract. Although we have not finished our quantitative estimations we are glad to report that a young guinea pig may live about two months and probably indefinitely on a diet of sprouted barley and dry oats without symptoms of scurvy whereas controls died in three weeks. Since this diet is probably deficient in salts and proteins and fat soluble A, we are repeating the experiments with the addition of condensed milk. Malt extract is often recommended for babies and nursing mothers, but the malt is kiln-dried and the wort is boiled and hence the extract is deficient in antiscorbutics. It seems evident that the only source of antiscorbutics in mother's milk is in the mother's diet. The use of malt extract prepared by our method might avoid the necessity of feeding orange juice to infants when oranges are very difficult to obtain.

Owing to the discrepancy between the results of Weill and Fuerst on the age of sprouting barley at which the antiscorbutic property appears, it is important to note that these authors did not record the temperature and by raising the temperature the barley may be made to sprout four times as fast as it does in most breweries. We found that the malt had little antiscorbutic power before the acrospire projected beyond the grain but had marked antiscorbutic power when the acrospire projected to a distance equal the length of the grain.

*The electric conductivity and polarization of skeletal muscle.* J. F. MC-  
CLENDON and FERDINAND A. COLLATZ.

Our object was to make more accurate determinations of the electric conductivity of muscle than have been recorded. A Vreeland oscillator giving a pure sine wave of 1000 oscillations per second was used as the source of current, and this was cut down by means of a rheostat so as not to stimulate curarized muscle. Frog's muscles were packed in a glass tube having at each end a chamber containing a platinized gold electrode in Ringer's fluid, separated from the muscle by a gold grid. A Wheatstone bridge was made, having zero inductance. The capacity of the conductivity cell and muscle fibers was balanced by condensers made of pure gold plates immersed in water. A tuned telephone was used as zero-instrument. Since a tone-silence cannot be obtained unless the capacities are balanced, the method enabled us to estimate the capacities of the conductivity cell and muscle, and by subtracting the capacity of the cell, the capacity of the muscle was obtained. Since the muscle has considerable capacity and does not contain metallic plates, it must contain plates or membranes of non-conducting or poorly conducting substance. These membranes are evidently the seat of polarization in the muscle.

An attempt was made to determine the difference in conductivity of the stimulated and unstimulated muscle. By cutting out resistance at the oscillator the current could be caused to stimulate the muscle, but it was difficult to tell when stimulation occurred with the muscles packed in the tube. Curarized turtle's muscle was placed between two bright platinum discs that were rigidly fixed and which slightly squeezed the muscle. On stimulating the muscle its electric conductivity increased but the increase was less as the muscle became fatigued and might be 200 per cent in a fresh muscle and 10 per cent in a muscle that had been stimulated several minutes. The experiments were done in a constant temperature room but the temperature of the interior of the muscle could not be exactly controlled. The backs and edges of the platinum plates were paraffined. The contraction of the muscle changed the shape of the projecting edges of muscle. Notwithstanding the sources of error, we cannot explain the fact that the stimulated muscle is always at least 10 per cent more conducting than the unstimulated without assuming that the polarization within the muscle decreases on stimulation.

*Intra-cellular acidity in Valonia.* W. J. CROZIER.

The cells of the marine green alga *Valonia* are sufficiently large to permit the extraction of 3 cc., or in some cases more, fluid from the central vacuole of a single cell. In normal cells the reaction of this intracellular fluid, containing  $\text{CO}_2$  under considerable tension is  $\text{pH} = 5.9$ , and is maintained at this point regardless of the external reaction (between  $\text{pH} = 6.6$  to  $9.5$ ), so long as the cell is healthy. The death process is accompanied by an increased alkalinity, approaching that of the sea water ( $\text{pH} = 8.1$ ), and by the penetration of  $\text{SO}_4$  into the cell-sap.

*The control of the response to shading in the gill-plumes of Chromodoris.*

W. J. CROZIER.

Between  $15^\circ$  and  $32^\circ$  and in sunlight not too intense, the gill-plumes of *Chromodoris zebra* respond by contraction when they are shaded. This contraction, due to the activation of receptors locally contained, leads to the reflex retraction of the whole gill crown within its collared pocket. The degree of extension of the gill crown as a whole is a function of the light intensity, but is controlled through a separate set of receptors. The nudibranch is photokinetic.

The sensitivity of the plumes to shading is abolished when the alkalinity of the sea water is reduced to  $\text{pH} = 7.9 \pm$ , and the retraction of the gill crown is furthermore completely inhibited at an alkalinity slightly lower. At  $\text{pH} = 8.4$  the gills remain totally concealed. The "protective" reaction to shading is thus a response superimposed upon the simple system of fundamental activities (protrusion, retraction) which is concerned with regulating the gaseous exchange of the nudibranch.

*Postural activity of the empty stomach.* T. L. PATTERSON.

The experiments in this report were undertaken with the view of studying the postural activity of the empty stomach of the bullfrog. The balloon method was used and just enough air was introduced with a syringe to produce a constant pressure of 2 cm. in the manometer. The necessary pressure for animals measuring from twelve to thirteen inches was obtained with 10 cc. of air and this was used as the constant throughout the experiments.

After stomostomy and the obtaining of gastric hunger records, the animals were divided into three groups, namely: (1) Animals having both vagi sectioned with the splanchnics intact; (2) animals having the splanchnics cut with the vagi intact; and (3) animals with both the vagi and the splanchnics cut.

Section of both vagi or the vago-sympathetics in the neck of the frog with the splanchnics intact leads to an increase in the volume capacity of the stomach, since to obtain the constant pressure of 2 cm. in the manometer 15 cc. of air must now be used instead of 10, but this condition is only temporary. There is a complete reestablishment of the postural activity of the stomach which takes place rather suddenly on the tenth day following the cutting of the nerves. Exactly the same



phenomenon occurs after section of the splanchnic nerves with the vagi intact, but in this case there is a decrease in the volume capacity of the stomach, so that only 4 cc. of air are required to produce the constant pressure of 2 cm., but here again there is a complete reestablishment as above on the tenth day following the operation.

When both sets of extrinsic nerves are sectioned, thus isolating completely the stomach from the central nervous system, there is again an increased volume capacity of the stomach from the normal or 10 cc. level to 15 cc. from which there is only a partial recovery. Usually on the thirteenth day following the operation a drop from 15 to 13 cm. of air occurs but it never returns to the old level. Therefore, since the local reflex mechanism of the gastric wall is incapable of bringing about a complete physiological readjustment of the posturally acting stomach (empty) when completely isolated from the central nervous system, but is capable when partially isolated, it shows that both the extrinsic and intrinsic nervous mechanisms take part in the maintenance of the postural activity, and that the stomach when completely isolated develops in time, within itself, a new level of postural activity which as determined by volume capacity is greater than the normal.

*On the effect of antipyretics on the hearing.* D. I. MACHT, J. P. GREENBERG and S. ISAACS.

The effect of a large number of antipyretic drugs and their combinations was studied on the hearing of normal human subjects. The following drugs were utilized: acetanilid, acetphenetidin, pyramidon, antipyrin, lactophenin, melubrin, salol, aspirin, sodium salicylate and quinin. The following combinations were also studied: acetanilid plus sodium bicarbonate, acetanilid plus salol, acetphenetidin plus salol, antipyrin plus aspirin, antipyrin plus salol, acetanilid plus acetphenetidin, aspirin plus salol, and some others. It was found that some antipyretics decrease the acuity of hearing, while others increase it, and that certain combinations produce unexpected synergistic effects. Among the most interesting findings are the following:

Acetanilid, aspirin and salol each markedly decrease the acuity of hearing. Antipyrin, pyramidon and acetphenetidin all tend to render the hearing more acute. A combination of acetanilid with salol instead of decreasing the hearing actually renders it more acute. A very interesting observation is the one concerning the combination of acetanilid with sodium bicarbonate. It was found that while acetanilid definitely decreases the hearing, when given alone, and while sodium bicarbonate produces no change in the acuity of hearing when administered by itself, a combination of acetanilid with sodium bicarbonate actually increases the distance limit of hearing in the same subjects. Some experiments have been made with the object of explaining the latter phenomenon. The complete data will be published in the *Journal of Psychobiology*.



*Action of corpus luteum extracts on the movements of isolated genito-urinary organs.* D. I. MACHT and S. MATSUMOTO. •

The present authors have been engaged for some time in the study of the physiological action of various glandular extracts, and more particularly of their influence on the genito-urinary organs.

The authors have studied extracts of fresh corpora lutea of the sow, and also extracts of various commercial preparations of the desiccated corpus luteum substance in respect to their action on the vasa deferentia of the dog, cat, rabbit, guinea pig and the rat, and have found the most suitable and most sensitive preparation for testing the corpus luteum extracts to be a freshly excised vas deferens of the rat in Tyrode's solution. Such preparations, when treated with some corpus luteum extracts, may react by contractions in solutions corresponding to concentration of 1:2500 of the fresh gland, and they almost always react to concentrations of 1:1000 of the fresh gland. It was interesting to note that the vas deferens, though very sensitive to the effects of the corpus luteum, does not react to extracts of ovarian substance proper. As far as the authors have been able to gather other data, both experimental and clinical, it seems that the activity of corpus luteum extracts, as indicated by the vas deferens preparations, runs parallel to the activity of those preparations as indicated by the other data. This organ, therefore, seems to furnish a convenient method of comparing the physiological activity of various corpus luteum preparations and some criterion for the testing of various chemical principles derived therefrom. Complete data of the present investigation will appear in due time in the *Journal of Urology*.